The golden years

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Chapter 4

The changing trends and outcomes in renal replacement therapy: data from the ERA-EDTA Registry

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Abstract

Background: This study examines the time trends in incidence, prevalence, patient and kidney allograft survival and causes of death in patients receiving RRT in Europe.

Methods: Eighteen national or regional renal registries providing data to the ERA-EDTA Registry between 1998-2011 were included. Incidence and prevalence time trends between 2001-2011 were studied with Joinpoint and Poisson regression. Patient and kidney allograft survival and causes of death between 1998-2011 were analysed using Kaplan-Meier and competing risk methods and Cox regression.

Results: From 2001-2008, the adjusted incidence of RRT rose by 1.1% (95%CI: 0.6; 1.7) annually to 131 per million population (pmp). During 2008-2011, the adjusted incidence fell by 2.2% (95%CI: -4.2; -0.2) annually to 125 pmp. This decline occurred predominantly in patients aged 45-64, 65-74 and in the primary renal diseases diabetes mellitus type 1 and 2, renovascular disease and glomerulonephritis. Between 2001-2011, the overall adjusted prevalence increased from 724 pmp to 1032 pmp (+3.3% annually, 95%CI: 2.8; 3.8). The adjusted 5-year patient survival on RRT improved between 1998-2002 and 2003-2007 (adjusted hazard ratio [HRa] 0.85, 95%CI: 0.84; 0.86). Comparing these time periods, the risk of cardiovascular deaths fell by 25% (HRa 0.75, 95%CI: 0.74; 0.77). However the risk of malignant death rose by 9% (HRa 1.09, 95%CI: 1.03; 1.16) in patients ≥65 years.

Conclusion: This European study shows a declining RRT incidence; particularly in patients aged 45-64, 65-74 and secondary to diabetic nephropathy. Encouragingly the adjusted RRT patient survival continues to improve. The risk of cardiovascular death has decreased, though the risk of death from malignancy has increased in the older population.

Introduction

The establishment of RRT programmes in the 1960s for the management of ESRD provided the prospect of survival for a select few patients (50). The past fifty years have seen RRT programmes grow exponentially with an unprecedented number of patients now receiving dialysis or a kidney transplant. Due to the global epidemics of diabetes mellitus, obesity and hypertension, coupled with an aging population and a greater acceptance of these patient groups onto RRT programmes, the patient profile has changed, from predominantly young males with relatively few co-morbidities to older, multi-comorbid individuals (51, 52).

Studies have reported a changing RRT incidence from one of continuous growth, to a slowing and in some cases, declining rate (8, 53). However, the prevalence has continued to increase (8, 53) and survival on RRT has continued to improve (53, 54). Furthermore, the causes of death (COD) in patients with ESRD may be changing from primarily cardiovascular deaths to non-cardiovascular deaths (55, 56).

Using data from 18 European countries or regions providing data to the ERA-EDTA Registry this paper aims, firstly, to provide an update of the trends in the incidence and prevalence of patients with ESRD receiving RRT over the past decade. Secondly to determine if the trends in patient and kidney allograft survival and mortality rates from cardiovascular and non-cardiovascular disease have changed with time.

Methods

Eighteen national (Austria, Denmark, Finland, Greece, Iceland, Norway, Sweden, the Netherlands) or regional (Dutch- and French-speaking Belgium; UK: England, Wales; UK: Scotland and the Spanish regions of Andalusia, Asturias, Basque Country, Cantabria, Catalonia and Valencia) renal registries, providing individual patient data to the ERA-EDTA Registry between 1998-2011 were included in the study. In 2011, these renal registries had 100% coverage of the population within their corresponding region equating to a population of 158,478,739.

Incidence and prevalence analyses

To minimise the effects of late reporting by the renal registries the 2001-2011 analyses of incidence and prevalence were based on the ERA-EDTA Registry 2012 database. The incidence per million population (pmp) was defined as the number of patients starting RRT annually divided by the mid-year general population. The incidence pmp, of all

paediatric and adult patients commencing RRT between 2001-2011 was calculated, firstly by country or regional renal registry, secondly by primary renal disease and thirdly by age group (per million age-related population, pmarp). The incidence was standardised for the EU27 age and gender distribution in 2005 (57). The prevalence pmp (defined as the number of patients alive and receiving RRT on the 31st December of that year, divided by the mid-year general population), of all paediatric and adult patients receiving RRT during 2001 to 2011 was calculated by country or regional renal registry. Time trends of the incidence and prevalence were analysed using Joinpoint regression and the annual percentage change (APC) was computed using Poisson regression (58) provided by the Joinpoint regression program (59). Details of this method have been previously described (8).

Survival analyses

Survival analyses were restricted to adult patients (aged ≥20 years) commencing RRT, dialysis or receiving a first kidney transplant, between 1998-2002 (historic cohort) or 2003-2007 (recent cohort) with the end of follow-up period set at 31st December 2012.

Trends over time by treatment modality

For patient survival on RRT the starting point of the analysis was the date of onset of RRT and the event studied was death. Censored observations were recovery of renal function, loss to follow-up and the end of the follow-up period. For patient survival on dialysis the first day of dialysis was considered as the starting point. The event studied was death, the competing event was kidney transplantation and censored observations were recovery of renal function, loss to follow-up and the end of the follow-up period. For patient and graft survival after transplantation the first day of kidney transplantation was taken as the starting point. For patient survival after transplantation the event studied was death and censored observations were loss to follow-up and the end of the follow-up period. For graft survival the events studied were death and graft failure and censored observations were loss to follow-up and the end of the follow-up period.

The Kaplan-Meier method was used to calculate 5-year survival probabilities on RRT and patient and graft survival after kidney transplantation, for the recent (2003-2007) and historic (1998-2002) cohorts. The cumulative incidence competing risk (CICR) method was used to calculate the 5-year patient survival probability on dialysis (60). Cox regression analyses were used to compare the unadjusted and adjusted 5-year survival by treatment modality between the recent and historic cohorts (60). Adjustments were made for age, sex, country and primary renal disease. Additionally, in the transplantation analyses, we adjusted for kidney donor type (living versus deceased donors).

Trends over time by causes of death

The COD groups comprised of: cardiovascular disease, infection, malignancy, other or unknown/missing (see Supplementary Table 4.1 for the ERA-EDTA codes). The 5-year unadjusted risk of death from the specific COD was calculated using the CICR method (60). A Cox regression analysis was performed to obtain the 5-year relative risk of mortality from a specific COD for incident adult RRT patients between the historic (1998-2002) and recent (2003-2007) cohorts. In both the competing risk and Cox regression analysis, the starting point was the first day of RRT and the event studied was death from a specific COD. The other CODs were considered as competing events in the competing risk analyses and censored observations in the Cox regression analyses. Loss to follow-up and the end of the follow-up period were considered as censored observations in both analyses. Deceased patients without a recorded date of death were excluded from the analysis. These analyses were repeated for patients aged <65 years and ≥65 years, with the same adjustments performed as described in RRT survival analyses above.

Sensitivity analysis

For the trends over time by COD, two sensitivity analyses were performed. In the first circumstance data from eleven renal registries with less than 20% of COD categorised as unknown/missing were analysed. Second, deaths coded as "cardiac arrest/sudden death/unknown" (ERA-EDTA code 015) were grouped as unknown/missing rather than as cardiovascular deaths.

All analyses were performed using SAS 9.3 or Joinpoint 4.0.4 (59). A p-value of less than 0.05 was considered statistically significant.

Results

Trends in the incident rate of RRT, 2001-2011

The incidence of RRT pmp, standardised for age and gender of the EU27, is detailed in Table 4.1. For all countries/regions the absolute number of incident patients is presented in Supplementary Table 4.2. A total of 204,648 patients with ESRD commenced RRT between 2001 and 2011. For all countries combined, the incidence of RRT rose by 1.1% (95%CI: 0.6; 1.7) annually from 123.4 pmp in 2001 to 131.0 pmp in 2008. Thereafter the incidence fell by 2.2% (95%CI: -4.2; -0.2) annually to 124.8 pmp in 2011. The incidence rate in the majority of the individual countries/regions stabilised. Only Iceland and French-speaking Belgium showed a consistent increase. Finland, Scotland and the Spanish regions of Andalusia and Cantabria showed a decline, either throughout the whole period, or in recent years. Figure 4.1 shows the unadjusted incidence pmarp of RRT

Country / Region	Incidence by year, per million population, adjusted for age and gender distribution											Trend 1		Trend 2		Trend 3	
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Period 1	APC %	Period 2	APC %	Period 3	APC %
All	123.4	123.2	123.7	128.7	129.3	130.9	131.4	131.0	131.8	125.5	124.8	2001-08 ↑	1.1 (0.6; 1.7)	2008-11 ↓	-2.2 (-4.2; -0.2)		
Austria	142.3	138.9	143.3	162.5	154.4	160.5	154.6	151.6	148.6	135.6	135.9	2001-06 ↑	3.5 (0.5; 6.6)	2006-11 —	-2.8 (-5.6; 0.1)		
Belgium: Dutch-speaking[a]	158.5	169.8	169.4	172.8	174.1	181.6	176.7	178.5	191.0	177.9	167.9	2001-09 ↑	2.8 (1.8; 3.7)	2009-11 —	-4.7 (-12.3; 3.5)		
Belgium: French-speaking[a]	178.5	175.7	162.2	187.8	176.9	189.3	187.6	192.6	199.2	193.8	189.5	2001-11 ↑	1.4 (0.5; 2.3)				
Denmark	147.5	139.2	139.4	138.5	126.2	125.5	150.6	129.5	137.7	122.0	115.8	2001-11 —	-0.8 (-2.2; 0.7)				
Finland	93.4	94.7	97.0	97.2	96.1	86.2	91.0	93.2	81.6	81.0	79.9	2001-11 —	-1.0 (-2.0; 0.0)				
Greece	167.7	170.6	183.2	190.0	184.8	185.6	177.8	184.2	185.5	169.3	177.4	2001-04 ↑	6.0 (1.0; 11.7)	2004-11 —	0.5 (-0.8; 1.8)		
Iceland	97.8	96.8	94.4	92.8	84.2	86.5	97.8	92.5	116.4	136.0	123.8	2001-11 ↑	3.5 (1.0; 6.0)				
Norway	102.4	101.5	103.0	109.0	107.7	108.5	121.7	122.0	124.9	111.8	108.3	2001-09 ↑	2.9 (1.6; 4.2)	2009-11 —	-6.5 (-16.7; 4.9)		
Spain: Andalusia	127.3	138.8	136.5	140.9	142.5	140.3	130.9	134.8	128.5	125.3	120.4	2001-05 ↑	2.6 (0.0; 5.3)	2005-11 ↓	-2.0 (-3.3; -0.6)		
Spain: Asturias	117.6	120.0	113.0	140.6	105.5	110.9	110.5	110.8	115.2	106.4	118.7	2001-11 —	-0.2 (-2.0; 1.6)				
Spain: Basque Country	115.1	94.0	129.4	123.6	115.4	105.4	108.0	101.8	121.0	100.0	100.4	2001-11 —	-0.6 (-2.8; 1.6)				
Spain: Cantabria[a]	152.4	116.7	128.4	141.9	152.2	119.0	102.6	104.4	103.5	123.7	103.3	2001-11 ↓	-3.1 (-5.6; -0.6)				
Spain: Catalonia	143.8	148.6	151.6	141.2	150.4	135.1	145.1	146.5	150.8	133.3	131.1	2001-11 —	-0.9 (-1.8; 0.1)				
Spain: Valencia	149.1	160.1	155.9	167.6	148.1	155.7	150.5	139.8	145.1	145.4	133.9	2001-11 —	-1.0 (-1.9; 0.0)				
Sweden	126.6	128.3	121.5	120.8	118.9	126.9	125.5	119.6	122.6	117.9	118.6	2001-11 —	-0.2 (-0.8; 0.3)				
the Netherlands	106.2	109.2	110.5	113.0	114.6	118.6	120.2	126.2	123.0	121.0	118.9	2001-04 ↑	1.7 (0.7; 2.7)	2004-08 ↑	4.0 (3.0; 4.9)	2008-11 —	-0.6 (-1.5; 0.3)
United Kingdom: England/Wales[ab]	95.70	94.0	92.4	100.3	104.2	108.6	112.6	112.5	112.8	109.4	110.4	2001-03 —	-0.8 (-5.3; 3.9)	2003-07 ↑	4.9 (2.6; 7.2)	2007-11 —	-0.8 (-2.2; 0.5)
United Kingdom: Scotland	101. 2	111.1	119.8	113.9	122.7	113.9	108. 7	102.9	101.8	97.5	92.9	2001-05 —	3.5 (-0.2; 7.3)	2005-11 ↓	-4.4 (-6.3; -2.5)		

↑: increasing APC; ↓: decreasing APC; —: stable APC; a: Patients <20 years of age are not reported; b: The incidence figures for UK; England and Wales represent 69%, 72%, 76% and 83% of the general population in 2001, 2002, 2003 and 2004 respectively. From 2005 Wales has 100% coverage of the general population. England has 90% in 2005 and 90.9% in 2006 and 100% coverage from 2007 onwards.

Table 4.1. Incidence of RRT per million population during the period 2001-2011, standardised for age and gender distribution of the EU27, presented with the annual percentage change (APC) and 95% confidence interval.

by age group for all countries combined. Following a consistent increase, the incidence rate in the oldest age groups of 75-84 and ≥85 years stabilised during the second half of the decade. For patients aged 45-64 and 65-74 the stable incidence rate in the first half of the decade reverted to a decline in the second half.

Figure 4.2 shows the incidence pmp of RRT by primary renal disease standardised for age and gender of the EU27. The incidence of RRT due to diabetes mellitus type 1 (APC: -2.6%, 95%CI: -4.2; -1.0) and type 2 (APC: -2.3%, 95%CI: -4.4; -0.2), glomerulonephritis (APC: -2.4%, 95%CI: -3.5; -1.3) and renovascular disease (APC: -7.3%, 95%CI: -13.1; -1.1) declined during the second half of the decade. The incidence of RRT secondary to pyelonephritis declined steadily throughout the study period whereas the incidence of RRT secondary to adult polycystic kidney disease and hypertension remained unchanged. Within the incident RRT patients, primary renal diseases classified as missing increased throughout the time period (APC: 12.6%, 95%CI: 8.5; 16.8).

Trends in the overall prevalence of RRT, 2001-2011

The prevalence of RRT pmp standardised for age and gender of the EU27 is shown in Table 4.2. Overall, the prevalence rose by 3.3% annually (95%CI: 2.8; 3.8) from 724.0 pmp in 2001 to 1032.4 pmp in 2011. For most countries/regions, the prevalence rate increased, though the rate of increase declined over time. The prevalence rate in Denmark, Norway and Austria initially grew, but stabilised by the end of the decade. For all countries/regions the absolute number of prevalent patients increased (Supplementary Table 4.3).

Trends in survival over time, by treatment modality

The 5-year adjusted risk of death after the start of dialysis improved between the recent (2003-2007) and historic (1998-2002) cohorts, for all patients (Table 4.3). Following kidney transplantation the 5-year adjusted risk of patient death and graft loss fell for patients <65 years receiving a deceased donor transplant. Within the same age group, there was a non-significant improvement, in the 5-year adjusted risk of death or graft survival after receiving a living donor kidney transplant. In the ≥65 year old patient group there was no statistically significant difference in the 5-year risk of death or graft survival between the recent and historic cohorts.

Trends over time by causes of death

There were a total of 90,600 deaths: 31.4% from cardiovascular causes, 13.9% infective, 6.9% malignant, 20.3% other causes and 27.5% unknown/missing. The 5-year adjusted risk of death in RRT patients was lower in the recent cohort compared to the historic

Figure 4.1. Unadjusted incidence of RRT per million age related population overall and by age group. Significant changes in the annual percentage change (APC) and 95% confidence interval (95%CI) are indicated in the right hand panel.

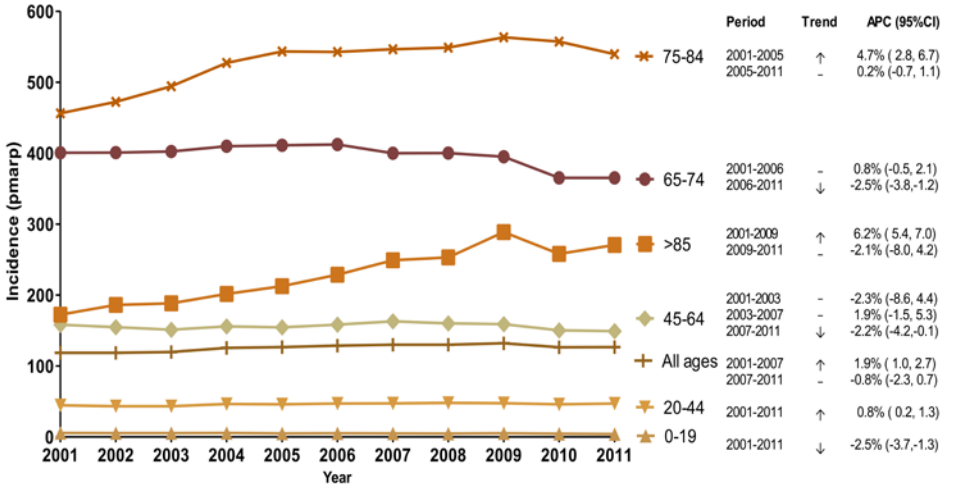
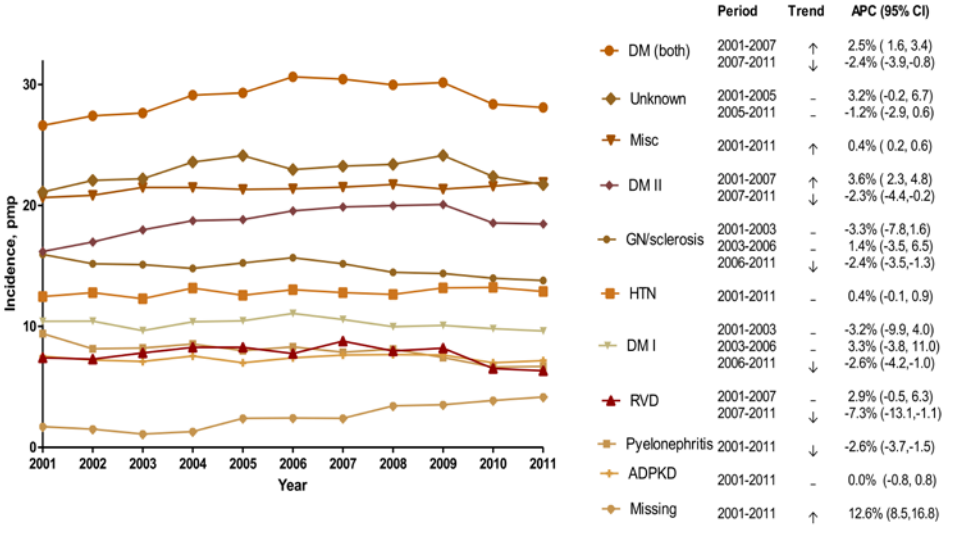


Figure 4.2. Age- and sex-adjusted incidence of incident RRT patients per million population between 2001-2011. Significant changes in the annual percentage change (APC) and 95% confidence interval (CI) are indicated in the right hand panel (DM: diabetes mellitus; GN: glomerulonephritis; ADPKD: autosomal dominant polycystic kidney disease; RVD: renovascular disease).



Country / Region	Prevalence by year, per million population, adjusted for age and gender distribution											Trend 1		Trend 2		Trend 3	
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Period 1	APC %	Period 2	APC %	Period 3	APC %
All	724.0	737.4	749.2	785.0	813.8	834.3	868.2	888.9	910.1	924.1	1032.4	2001-11 ↑	3.3 (2.8; 3.8)				
Austria	775.6	796.0	822.9	860.3	887.3	909.8	928.8	973.0	960.3	955.0	954.5	2001-08 ↑	3.2 (2.9; 3.6)	2008-11 —	-0.6 (-1.7; 0.6)	2009-11 ↑	1.4 (0.4; 2.4)
Belgium: Dutch-speaking[a]	830.6	861.8	885.8	914.7	946.9	975.9	998.9	1021.7	1051.3	1064.8	1079.6	2001-06 ↑	3.2 (3.0; 3.5)	2006-09 ↑	2.5 (1.4; 3.5)		
Belgium: French-speaking[a]	854.7	899.6	941.9	989.4	1020.1	1063.3	1096.1	1127.5	1164.8	1203.3	1230.5	2001-04 ↑	5.1 (4.2; 6.0)	2004-11 ↑	3.2 (3.0; 3.4)		
Denmark	693.5	721.0	745.7	766.4	774.4	783.2	821.3	828.6	838.5	837.2	840.1	2001-08 ↑	2.5 (2.0; 3.0)	2008-11 —	0.2 (-1.6; 2.1)		
Finland	619.9	640.5	663.9	682.3	704.8	711.6	725.0	741.8	749.3	757.6	760.1	2001-05 ↑	3.3 (2.6; 4.0)	2005-11 ↑	1.4 (1.0; 1.7)		
Greece	826.1	851.8	893.2	891.2	914.9	928.7	944.0	960.1	978.4	980.3	989.1	2001-03 ↑	3.8 (1.0; 6.7)	2003-11 ↑	1.5 (1.2; 1.7)	2006-11 ↑	6.3 (2.9; 9.7)
Iceland	477.7	513.7	567.6	554.4	546.3	546.6	583.2	593.2	618.8	683.0	747.3	2001-03 —	9.0 (-7.6; 8.5)	2003-06 —	-1.6 (-5.9; 15.0)		
Norway	652.8	681.4	712.2	751.0	771.0	791.1	820.1	853.3	878.9	889.9	901.9	2001-04 ↑	4.6 (3.6; 5.7)	2004-09 ↑	3.3 (2.7; 3.9)	2008-11 ↑	1.9 (0.6; 3.2)
Spain: Andalusia	881.4	925.1	953.8	983.3	1014.8	1011.7	993.3	1007.8	1025.5	1045.8	1056.0	2001-05 ↑	3.4 (2.5; 4.3)	2005-08 —	-0.4 (-3.0; 2.3)		
Spain: Asturias	729.3	750.1	761.4	806.6	823.1	830.0	827.4	836.8	846.8	847.7	874.4	2001-05 ↑	3.0 (1.8; 4.3)	2005-11 ↑	0.9 (0.2; 1.5)		
Spain: Basque Country	803.9	810.1	844.4	878.3	913.5	917.3	931.2	938.5	967.2	975.1	995.1	2001-05 ↑	3.3 (2.4; 4.3)	2005-11 ↑	1.5 (1.1; 2.0)		
Spain: Cantabria[a]	745.6	731.7	773.1	808.9	806.4	800.6	795.5	807.5	828.5	851.1	874.8	2001-11 ↑	1.5 (1.0; 1.9)				
Spain: Catalonia	1019.2	1034.2	1052.5	1083.7	1075.1	1073.9	1110.6	1138.1	1163.3	1176.2	1181.9	2001-11 ↑	1.5 (1.3; 1.8)				
Spain: Valencia	1057.3	1076.0	1069.4	1106.4	1088.4	1096.5	1102.1	1094.4	1102.6	1116.8	1116.9	2001-11 ↑	0.5 (0.3; 0.7)				
Sweden	743.8	765.8	777.1	796.4	808.4	831.6	845.0	851.6	864.4	879.0	892.4	2001-06 ↑	2.2 (1.9; 2.5)	2006-11 ↑	1.4 (1.2; 1.7)		
the Netherlands	655.9	681.6	697.9	719.9	746.5	778.3	798.2	826.7	854.2	871.1	883.6	2001-09 ↑	3.4 (3.2; 3.5)	2009-11 ↑	1.7 (0.3; 3.2)	2009-11 —	1.4 (-0.4; 3.1)
United Kingdom: England/Wales[ab]	581.54	585.17	578.89	653.32	678.22	707.43	783.83	809.47	837.13	855.87	879.0	2001-11 ↑	4.9 (4.1; 5.6)				
United Kingdom: Scotland	671.3	693.4	717.1	728.0	754.4	773.4	797.6	807.3	822.0	829.0	830.7	2001-07 ↑	2.9 (2.6; 3.2)	2007-11 ↑	1.1 (0.6; 1.7)		

↑: increasing APC; —: stable APC; a: Patients <20 years of age are not reported; b: The incidence figures for UK; England and Wales represent 69%, 72%, 76%, and 83% of the general population in 2001, 2002, 2003 and 2004 respectively. From 2005 Wales has 100% coverage of the general population. England has 90% in 2005 and 90.9% in 2006 and 100% coverage from 2007 onwards.

Table 4.2. Prevalence of RRT per million population during the period 2001-2011, standardised for age and gender distribution of the EU27, presented with the annual percentage change (APC) and 95% confidence interval.

	Cohort	All patients				<65 years				>65 years			
		N	5-year survival (95%CI)	Crude HR (95%CI)	Adjusted HR (95%CI)	N	5-year survival (95%CI)	Crude HR (95%CI)	Adjusted HR (95%CI)	N	5-year survival (95%CI)	Crude HR (95%CI)	Adjusted HR (95%CI)
Patient survival on RRT from day 1													
RRT	2003-2007	91224	46.8 (46.5; 47.1)	0.95 (0.94; 0.97)	0.85 (0.84; 0.86)	40623	69.7 (69.2; 70.1)	0.91 (0.88; 0.93)	0.85 (0.83; 0.88)	50601	28.4 (27.9; 28.7)	0.92 (0.90; 0.93)	0.86 (0.84; 0.87)
	1998-2002	70503	45.0 (44.6; 45.4)	1	1	33683	66.6 (66.0; 67.1)	1	1	36820	25.2 (24.7; 25.6)	1	1
Patient survival on dialysis from day 1													
Dialysis[a]	2003-2007	89019	48.5 (43.5; 50.1)	0.93 (0.92; 0.95)	0.85 (0.84; 0.87)	38583	71.3 (65.0; 72.4)	0.88 (0.85; 0.90)	0.84 (0.82; 0.87)	50436	31.0 (24.7; 32.7)	0.91 (0.90; 0.93)	0.86 (0.84; 0.87)
	1998-2002	69337	47.1 (41.9; 49.5)	1	1	32583	69.1 (63.7; 73.5)	1	1	36754	27.8 (21.1; 30.1)	1	1
Patient survival after the first renal transplant													
All	2003-2007	19673	87.8 (87.3; 88.3)	0.93 (0.87; 0.99)	0.86 (0.81; 0.91)	16988	90.6 (90.2; 91.0)	0.86 (0.80; 0.92)	0.82 (0.76; 0.88)	2685	70.3 (68.5; 72.0)	0.97 (0.87; 1.09)	0.96 (0.86; 1.08)
	1998-2002	14784	86.9 (86.3; 87.4)	1	1	13145	89.1 (88.5; 89.6)	1	1	1639	69.5 (67.2; 71.7)	1	1
Living donor	2003-2007	4065	93.8 (93.0; 94.5)	0.92 (0.76; 1.12)	0.78 (0.64; 0.96)	3802	94.8 (94.0; 95.4)	0.89 (0.72; 1.11)	0.80 (0.64; 1.00)	263	79.9 (74.5; 84.2)	0.81 (0.51; 1.28)	0.81 (0.49; 1.34)
	1998-2002	2436	93.2 (92.1; 94.1)	1	1	2317	94.1 (93.0; 95.0)	1	1	119	76.5 (67.8; 83.1)	1	1
Deceased donor	2003-2007	14814	85.9 (85.4; 86.4)	0.97 (0.91; 1.03)	0.88 (0.82; 0.94)	12455	89.1 (88.6; 89.7)	0.89 (0.82; 0.97)	0.84 (0.77; 0.91)	2359	69.1 (67.2; 70.9)	0.99 (0.88; 1.11)	0.99 (0.88; 1.12)
	1998-2002	11555	85.4 (84.8; 86.1)	1	1	10099	87.9 (87.2; 88.5)	1	1	1456	68.6 (68.6; 70.9)	1	1
Graft survival after the first renal transplant													
All	2003-2007	20470	79.6 (79.0; 79.1)	0.95 (0.91; 0.99)	0.91 (0.87; 0.96)	17675	82.1 (81.5; 82.6)	0.90 (0.86; 0.95)	0.89 (0.85; 0.94)	2795	63.7 (61.9; 65.4)	1.01 (0.92; 1.12)	
	1998-2002	15478	78.5 (77.8; 79.1)	1	1	13805	80.3 (79.6; 80.9)	1	1	1673	63.8 (61.4; 66.0)	1	1
Living donor	2003-2007	4182	87.3 (86.2; 88.2)	0.92 (0.81; 1.01)	0.89 (0.77; 1.01)	3909	88.0 (86.9; 88.9)	0.91 (0.79; 1.05)	0.89 (0.77; 1.03)	273	77.3 (71.8; 81.8)	0.82 (0.53; 1.25)	0.77 (0.48; 1.22)
	1998-2002	2544	86.1(84.7; 87.4)	1	1	2422	86.8 (85.3; 88.0)	1	1	122	73.8 (65.0; 80.7)	1	1
Deceased donor	2003-2007	15493	77.3 (76.6; 78.0)	0.99 (0.94; 1.04)	0.93 (0.88; 0.98)	13034	80.2 (79.5; 80.9)	0.94 (0.89; 0.99)	0.90 (0.85; 0.96)	2459	62.0 (60.0; 63.9)	1.04 (0.94; 1.16)	1.03 (0.92; 1.14)
	1998-2002	12141	77.0 (76.2; 77.7)	1	1	10654	79.0 (78.1; 79.7)	1	1	1487	62.9 (60.4; 65.3)	1	1

a: Survival on dialysis was examined using the cumulative incidence competing risk method, with transplantation as competing risk.

Table 4.3. Five-year survival probabilities, unadjusted and adjusted hazard ratios, with 95% confidence intervals (CI) for patient survival from day 1, after starting RRT, dialysis or receiving a first renal transplant and first graft survival for 1998-2002 and 2003-2007 cohorts for all patients and for patients under and over 65 years.

Cause of death	Cohort	All patients			<65 years			≥65 years		
		Risk of dying from specific COD (95%CI)	Crude HR (95%CI)	Adjusted HR (95%CI)	Risk of dying from specific COD (95%CI)	Crude HR (95%CI)	Adjusted HR (95%CI)	Risk of dying from specific COD (95%CI)	Crude HR (95%CI)	Adjusted HR (95%CI)
All deaths	2003-2007	53.2 (53.0; 53.4)	0.95 (0.94; 0.96)	0.85 (0.84; 0.89)	30.3 (30.2; 30.5)	0.89 (0.86; 0.91)	0.84 (0.82; 0.86)	71.7 (71.4; 71.9)	0.92 (0.90; 0.93)	0.85 (0.84; 0.87)
	1998-2002	55.0 (54.8; 55.1)	1	1	33.5 (32.3; 33.6)	1	1	74.8 (74.5; 75.2)	1	1
Cardiovascular disease	2003-2007	15.9 (13.5; 18.3)	0.81 (0.78; 0.83)	0.75 (0.74; 0.77)	9.1 (6.3; 11.9)	0.74 (0.71; 0.78)	0.74 (0.71; 0.77)	21.3 (17.7; 24.9)	0.78 (0.76; 0.81)	0.77 (0.74; 0.79)
	1998-2002	19.4 (16.5; 22.3)	1	1	12.0 (8.5; 15.5)	1	1	26.1 (21.6; 30.6)	1	1
Infection	2003-2007	7.7 (6.0; 9.4)	0.98 (0.94; 1.01)	0.91 (0.88; 0.95)	4.5 (2.5; 6.5)	0.87 (0.81; 0.93)	0.87 (0.82; 0.93)	10.3 (7.6; 12.9)	0.97 (0.93; 1.01)	0.94 (0.90; 0.98)
	1998-2002	7.8 (5.8; 9.7)	1	1	5.1 (2.7; 7.5)	1	1	10.2 (7.1; 13.3)	1	1
Malignancy	2003-2007	3.9 (2.6; 5.2)	1.04 (0.99; 1.10)	1.03 (0.98; 1.08)	2.4 (0.9; 3.6)	0.92 (0.84; 1.01)	0.96 (0.88; 1.06)	5.1 (3.1; 7.0)	1.04 (0.98; 1.11)	1.09 (1.03; 1.16)
	1998-2002	3.7 (2.3; 5.1)	1	1	2.6 (0.9; 4.3)	1	1	4.7 (2.5; 6.8)	1	1
Other	2003-2007	10.9 (8.9; 13.0)	0.93 (0.90; 0.96)	0.84 (0.81; 0.86)	5.3 (3.1; 7.5)	0.88 (0.82; 0.93)	0.85 (0.80; 0.91)	15.5 (12.3; 18.6)	0.88 (0.85; 0.91)	0.83 (0.80; 0.86)
	1998-2002	11.6 (9.2; 14.0)	1	1	5.9 (3.4; 8.4)	1	1	16.8 (13.0; 20.6)	1	1
Unknown/ Missing	2003-2007	13.6 (11.4; 15.8)	1.17 (1.14; 1.20)	0.90 (0.88; 0.93)	8.4 (5.7; 11.1)	1. 14 (1.09; 1.20)	0. 91 (0.87; 0.96)	17.7 (14.4; 21.1)	1.11 (1.08; 1.15)	0.90 (0.87; 0.94)
	1998-2002	11.5 (9.1; 13.8)	1	1	7.2 (4.4; 10.0)	1	1	15.3 (11.6; 19.0)	1	1

Table 4.4. Five-year probability of death, and unadjusted and adjusted hazard ratios (HR), by cause of death, with 95% confidence intervals (95%CI) for patients after starting RRT, 1998-2002 and 2003-2007 cohorts for all patients and for patients under and over 65 years.

cohort for each COD, with the exception of the risk of death from malignancy (Table 4.4). The greatest reduction was seen in the adjusted risk of cardiovascular deaths which was 25% (HRa 0.75, 95%CI: 0.74; 0.77) lower in the recent cohort. For patients <65 years, the risk of death from malignant causes remained unchanged (HRa 0.96, 95%CI: 0.88; 1.06) but rose by 9% in patients ≥65 years (HRa 1.09, 95%CI: 1.03; 1.16).

A sensitivity analysis was performed on the data supplied by eleven renal registries with <20% of deaths recorded as unknown/missing. Within this subgroup, the adjusted risk of death for all patients was similar to the main analyses. However, when analysing by age group, there were no longer statistically significant changes between the two cohorts in the risk of death from infectious causes in the <65 year olds (HRa 0.95, 95%CI: 0.85; 1.08) or malignant causes in the ≥65 year olds (HRa 1.09, 95%CI: 0.99; 1.20). Moving "cardiac arrest/sudden death/unknown" from cardiovascular to unknown COD did not alter the results.

Discussion

This study details the changing epidemiology of patients with ESRD receiving RRT in 18 European countries or regions over the past decade. The overall incidence has declined by 2.2% annually. This is predominantly due to a decrease in the incidence of RRT in the 45-64 and 65-74 year old groups, a stabilisation in the ≥75 year old groups and a decline in the incidence of RRT secondary to diabetes mellitus type 1 and 2, renovascular disease and glomerulonephritis. Remarkably this has occurred despite the ongoing epidemics of diabetes mellitus, obesity and hypertension in the general population. The prevalence rate of RRT for most countries has continued to grow albeit at a declining rate, and, for the first time, stabilised in three countries. Patient survival on dialysis at 5 years, has improved between the historic (1998-2002) and recent (2003-2007) cohorts. The 5-year adjusted risk of death and graft survival following a deceased donor kidney transplant has improved, and there has been a non-significant improvement in graft survival from a living donor transplant. In line with other studies we report a decline in the adjusted risk of cardiovascular deaths over time within the RRT population.

Trends in the incident rate of RRT, 2001-2011

The decline in the incidence of RRT in Europe is in accordance with data recently reported from the US and Canada (61, 62). While the decline could be attributed to a fall in the number of patients reaching CKD stage 5, there are several other potential explanations. It is possible that in recent years nephrologists' attitudes towards the initiation of RRT may have changed. Previous conventional wisdom suggested commencing RRT with a

higher GFR was associated with a survival advantage (63), prompting a trend towards ever higher GFRs at the start of RRT. The commencement of RRT at higher GFRs was particularly evident in diabetics and older patients (64-66). Over the past decade, evidence questioning this notion (67-70), along with a change in guidance (71-73) may have resulted in a modification of clinical practice. The United States Renal Data System showed a decline in the incidence of early starters to dialysis from 2008 (74). As we do not have data detailing the GFR, we cannot clarify if the decline in incidence is directly related to lower GFRs at dialysis initiation.

Although the incidence of RRT in the older patient groups has recently declined, historical publications showing no harm in dialysing elderly patients (75) had previously led to a dramatic rise in the acceptance of elderly patients onto RRT programmes (76). Recent studies have not demonstrated a clear survival benefit of haemodialysis compared to conservative care in the elderly (77). This, in conjunction with a trend toward increased consideration of conservative care programmes (71, 78), or the later initiation of dialysis could partly explain the stabilisation of incidence rates in the older age groups.

Worldwide the incidence of diabetes mellitus type 1 and 2 is rising (79), despite this we have shown a decline in the RRT incidence in patients with diabetic nephropathy. Similar findings have recently been reported elsewhere (61, 74, 80). Health improvement initiatives such as screening for diabetes mellitus and its sequelae (81, 82), improved metabolic control and the increased use of renin-angiotensin system blockers (80) may be responsible for the delay in the progression of diabetic nephropathy to ESRD (52, 83, 84). In accordance with this rationale, the incidence of other diabetic microvascular complications such as retinopathy is also declining (85). It must be noted however, that a large proportion of patients were coded with an "unknown" primary renal disease. Patients with diabetes mellitus are likely to have their renal function monitored and therefore unlikely to present with ESRD classified as unknown. Nonetheless, a degree of caution is required in interpreting the results.

Of note, the latter half of the last decade bore witness to the European economic crisis. Subsequent austerity measures may have resulted in health care reform strategies focusing primarily on cost containment (86). In some cases, the cost containment could have resulted in reduced access to RRT, thus contributing to the decline in the incidence of RRT. Though studies specifically addressing this are required.

Trends in the prevalence rate of RRT, 2001-2011

The continuing rise in prevalence rate of RRT albeit with a slower rate of growth is consistent with an earlier study from the ERA-EDTA Registry (8) and a recent United States Renal Data System report (61). The recent stabilisation of the Austrian, Danish and Norwegian prevalence rates are notable exceptions. Although, these results show, for the first time, stable prevalence rates within European countries, a longer time frame is required to determine whether this a true trend and/or will extend to the rest of Europe. Furthermore, it should be noted, that even in these countries, the absolute number of prevalent patients continues to grow.

Trends in survival on RRT, 1998-2002 versus 2003-2007

We have shown that over the past decade patient survival dialysis has improved which is in line with findings from the US (61). The improvement in dialysis survival may reflect advances in dialysis techniques, however this, particularly in haemodialysis patients, remains unfounded (87).

There was a significant improvement in the adjusted 5-year risk of graft failure in those <65 years, following a deceased donor kidney transplant and a non-significant improvement in the adjusted risk of graft failure following a living donor kidney transplant. The improvement in deceased donor transplant outcomes may be surprising in view of the increased use of marginal donors (88-90). However, advances in transplantation medicine may have counterbalanced the increased use of marginal kidneys. Despite increasing transplant waiting list times, overall advances in patient care, may have led to a relatively fitter subset of patients at the time of transplantation, which may have contributed to the improvement in deceased donor transplant outcomes.

Kidney transplantation in patients ≥65 years old has changed from a relatively exclusive event in a highly selected few, to a reality for a substantial proportion of RRT patients (91, 92). The increased acceptance of older patients may have resulted in a greater proportion of transplant recipients with multiple co-morbidities. These changes in case mix could explain the lack of improvement in graft survival among the most recent cohort, however, our data does not allow for this to be assessed. Although kidney transplantation is becoming an accepted form of RRT in the elderly, the sample size is still relatively small. This may explain the lack of significant outcomes in this age group.

Trends in mortality rates and causes of death, 1998-2002 versus 2003-2007

In accordance with other studies we found the decline in mortality in patients on RRT over time is predominantly due to a reduction in cardiovascular deaths (93). This was seen

in both patients <65 and ≥65 years. Public health initiatives to reduce cardiovascular risk factors have led to a decline in cardiovascular mortality in the general population (94). However, due to the complex aetiology responsible for cardiovascular disease within the RRT patient group (95), it cannot be inferred that these initiatives are responsible for the reduction in cardiovascular mortality observed in this study (96). As such, the specific interventions responsible for the decline in cardiovascular mortality rate in dialysis patients requires further investigation (97).

It is recognised that a chronic uraemic state increases the risk of malignancy (98), however the previously higher rate of cardiovascular mortality in RRT patients may have concealed this increased risk. Historically the high cardiovascular mortality rates may have inhibited the perceived benefits and cost-effectiveness of cancer screening within this patient group (99). The benefits of cancer screening in patients receiving RRT may need to be revisited in light of these findings. It is also possible that oncology patients are now surviving treatment for malignancy albeit with sequelae such as ESRD (100-102). Despite their initial survival these patients may still be at increased risk of death from the underlying malignancy (103) which may explain the rise in mortality from malignant causes in the RRT population. It should be noted however that a large proportion of COD in this study are coded as unknown/missing, which necessitates caution when interpreting the COD findings.

Conclusion

Over the past decade we have seen changes in the profile of patients undergoing RRT for ESRD in Europe. The incidence rate of RRT for ESRD is declining; particularly in patients aged 45-64 and 65-74 years and in those with a primary renal disease of diabetes mellitus type 1 and 2, renovascular disease and glomerulonephritis. In addition, for the first time the incidence of patients ≥75 years has stabilised. Though further research is required to clarify to what degree these changes represent a reduction in the number of patients reaching CKD stage 5 or reflect changes in modern clinical practice patterns.

After decades of continuous growth, the prevalence rate although still increasing has started to slow. The changing trend in the prevalence of RRT detailed in this study could guide future projections of RRT burden in Europe and therefore aid future national resource planning.

Finally, whilst it is comforting to see mortality rates from cardiovascular disease fall, both the rise in malignant deaths in patients aged ≥65 years and the lack of improvement in kidney allograft survival in this age group highlights the need for further research into the older adult on RRT.

Supplementary Table 4.1. ERA-EDTA codes included in the cause of death groups.

Cause of death	Causes of death included with ERA-EDTA code in brackets
Cardiovascular	myocardial ischaemia (11), hypertensive cardiac failure (16), other causes cardiac failure (14), haemorrhagic pericarditis (13), haemorrhage from ruptured vascular aneurysm (26), cerebro-vascular accident (22), mesenteric infarction (29), cardiac arrest/sudden death/unknown (15)
Infective causes	pulmonary infection: bacterial (31), pulmonary infection: viral (32), pulmonary infection: fungal or protozoal-parasitic (33), infections elsewhere except viral hepatitis (34), septicaemia (35), pulmonary tuberculosis (36), tuberculosis elsewhere (37), generalised viral infection (38), liver disease due to hepatitis B virus (41), liver disease due to other viral hepatitis (42), peritonitis all causes except peritoneal dialysis (39), peritonitis: bacterial, with peritoneal dialysis (100), peritonitis: fungal, with peritoneal dialysis (101)
Malignant disease	malignant disease possibly induced by immunosuppressive therapy (66), malignant disease: solid tumours except those of 66 (67), malignant disease: lymphoproliferative disorders except those of 66 (68)
Other	gastrointestinal haemorrhage (23), perforation of peptic ulcer (71), perforation of colon (72), pancreatitis (62), liver disease due to drug toxicity (43), cirrhosis- not viral (44), cystic liver disease (45), liver failure- cause unknown (46), hypokalaemia (17), fluid overload /pulmonary oedema (18), pulmonary embolus (21), haemorrhage from surgery (27), other haemorrhage (28), suicide (52), bone marrow depression (63), cachexia (64), dementia (69), chronic obstructive airways disease (73), accident unrelated to ESRD treatment (82), haemorrhage from graft site (24), haemorrhage from vascular access/ dialysis circuit (25), peritonitis: due to other cause with PD (102), peritonitis: sclerosing, with peritoneal dialysis (70), accident related to ESRD treatment: not code 25 (81), hyperkalaemia (12), ESRD treatment ceased for any other reason (53), ESRD treatment withdrawn for medical reasons (54), patient refused further treatment for ESRD (51), uraemia caused by graft failure (61), other identified cause of death (99)
Unknown/missing	Cause of death uncertain/not determined (0)

Country / Region	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Austria	1105	1089	1134	1303	1251	1318	1275	1248	1259	1173	1189
Belgium: Dutch-speaking[a]	950	1033	1045	1090	1112	1180	1164	1191	1293	1233	1170
Belgium: French-speaking[a]	746	744	694	815	772	830	830	857	900	882	868
Denmark	746	705	713	719	663	663	809	700	752	678	655
Finland	474	489	497	508	509	457	497	508	451	455	461
Greece	1829	1851	1986	2180	2162	2207	2145	2263	2313	2157	2297
Iceland	22	22	21	23	20	21	26	23	28	34	33
Norway	426	422	436	463	460	466	531	537	562	509	504
Spain: Andalusia	830	906	902	939	961	1002	977	1030	995	989	961
Spain: Asturias	148	144	138	177	131	145	143	144	149	140	156
Spain: Basque Country	248	205	284	276	261	241	253	241	285	240	243
Spain: Cantabria[a]	85	67	72	82	90	72	64	65	64	76	65
Spain: Catalonia	917	971	1012	947	1041	954	1041	1061	1115	995	987
Spain: Valencia	612	675	683	741	675	735	728	690	735	747	701
Sweden	1132	1158	1101	1108	1097	1184	1180	1132	1180	1141	1166
the Netherlands	1570	1595	1626	1683	1732	1809	1865	1985	1964	1955	1964
United Kingdom: England/Wales[a b]	3003	3396	3556	4304	4704	5147	5885	5955	6044	5930	6073
United Kingdom: Scotland	492	546	594	569	619	578	558	532	534	510	496

a: Patients younger than 20 years of age are not reported; b: The incidence figures for UK; England and Wales represent 69%, 72%, 76% and 83% of the general population in 2001, 2002, 2003 and 2004 respectively. From 2005 Wales has 100% coverage of the general population. England has 90% in 2005 and 90.9% in 2006 and 100% coverage from 2007 onwards.

Supplementary Table 4.2. Incidence counts of renal replacement therapy for end-stage renal disease at day 1, during the period 2001-2011.

Country / Region	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Austria	6070	6314	6558	6929	7231	7512	7732	7899	8189	8320	8429
Belgium: Dutch-speaking[a]	4974	5237	5457	5720	6004	6279	6527	6779	7080	7289	7488
Belgium: French-speaking[a]	3526	3750	3944	4202	4370	4601	4800	4991	5215	5447	5650
Denmark	3637	3807	3964	4111	4190	4276	4524	4613	4708	4751	4823
Finland	3186	3326	3469	3605	3759	3833	3956	4090	4176	4269	4340
Greece	9019	9335	9766	10266	10698	11023	11363	11688	12062	12246	12466
Iceland	116	125	139	140	143	148	161	167	173	191	213
Norway	2764	2919	3050	3256	3387	3512	3694	3897	4077	4202	4334
Spain: Andalusia	5747	6101	6366	6640	6930	7330	7549	7810	8089	8384	8604
Spain: Asturias	855	883	908	972	1003	1025	1027	1053	1072	1085	1124
Spain: Basque Country	1730	1764	1855	1948	2046	2094	2158	2201	2293	2334	2409
Spain: Cantabria[a]	407	405	423	449	474	485	488	502	523	543	563
Spain: Catalonia	6472	6713	7006	7261	7448	7650	7959	8297	8621	8834	8998
Spain: Valencia	4326	4535	4675	4914	5010	5209	5359	5488	5648	5805	5909
Sweden	6599	6852	7005	7250	7442	7752	7952	8086	8308	8555	8798
the Netherlands	10078	10440	10792	11240	11762	12369	12833	13456	14086	14549	14982
United Kingdom: England/Wales[a b]	18366	21266	22446	28225	30913	33847	41383	43199	45201	46791	48642
United Kingdom: Scotland	3210	3350	3485	3578	3738	3864	4014	4096	4198	4277	4337

a: Patients younger than 20 years of age are not reported; b: The prevalence figures for UK; England and Wales represent 69%, 72%, 76% and 83% of the general population in 2001, 2002, 2003 and 2004 respectively. From 2005 Wales has 100% coverage of the general population. England has 90% in 2005 and 90.9% in 2006 and 100% coverage

Supplementary Table 4.3. Prevalence counts of renal replacement therapy for end-stage renal disease during the period 2001-2011.