Chapter 15: Causes of Death on Renal Replacement Therapy

Summary

- Cardiovascular disease is the most common cause of death in the renal population and is most evident in diabetics.

- Patients on renal replacement therapy have a much higher relative risk of death compared with the general population. This is most pronounced in the young and diminishes with longevity.

- Underlying primary renal diagnosis affects the death rate. Cystic/polycystic patients have the lowest rate of death, patients with malignancy the highest.

- The UK compares favourably with other international Renal Registries when assessing causes and rates of death, although USA patients under 65 years of age have a significantly lower death rate than those in the UK. The comparisons have not been adjusted for the higher ethnic minority component in the USA, who are known to have better survival.

Introduction

This is the first analysis of cause of death for patients on the UK Renal Registry. This work has been partly funded through a grant from the National Kidney Research Fund.

There have been 11,607 deaths reported since the Registry was started in 1997, 6237 (54%) having a cause recorded coded from the European Dialysis and Transplant Association (EDTA) diagnostic list for causes of death (Table 15.1).

Many centres do not return a cause of death to the Registry, and it is not a mandatory field. The percentage completeness by centre of the returns for causes of death has remained constant over the years, indicating that there has been no change at the centre level in the practice of completion of this item.

An initial analysis limited to centres with a high rate of return for cause of death, compared with an analysis of all the cause of death data on the database, showed that the percentages in corresponding EDTA categories remained unchanged if the latter data were included.

The EDTA codes of death were grouped into the categories (see Table 15.28):

1. cardiovascular disease
2. cerebrovascular disease
3. infection
4. malignancy
5. treatment withdrawal
6. others
7. uncertain or not determined

The data for all prevalent patients on renal replacement therapy (RRT) since the inception of the UK Renal Registry to 2001 and with a recorded cause of death were analysed initially by treatment modality (dialysis or transplant; see Appendix F). Subgroup analysis for both incident and prevalent patients, in conjunction with the relationship of age, primary diagnosis and gender to the cause of death, were then examined. For the incident cohort, an analysis of the interaction between comorbidity at the start of RRT and cause of death was also undertaken. The ethnicity data were too incomplete to be included. The primary diagnoses for cause of renal failure categorised by EDTA coding were grouped into 10 categories (see Appendix F).

The incident cohort included all patients starting RRT since individual renal units joined the Registry. Transplanted patients were excluded from the analysis in the incident cohort because of the small number transplanted in this group (fewer than 100 per year) and very low death rate. The subgroup prevalent cohort of patients were defined as those on dialysis on or before 30 September 01 and alive on 31 December 01.

Comparisons of the data were made with the general population of England & Wales and also with data from other international Renal Registries. The two-tailed Student 't' test was used for testing significance.

Prevalent patients from 1998 to 2001

By EDTA code for cause of death, the most common cause of death in the dialysis population was myocardial ischaemia or infarction (n=872, 17.7%; see Appendix F), closely followed by 'uncertain' or 'not identified' (n= 758, 15.4%). In the transplant population, these were again the two most common causes, accounting for 22.2% and 10.5% of deaths respectively (see Appendix F). The EDTA codes were regrouped as outlined above, and cardiovascular disease remained the most common cause of death in both the transplant and dialysis populations (37% and 31% respectively; Table 15.1). Using the two-tailed Student 't' test, the effect of cardiovascular disease appeared greater in the transplant population; this may have been due to the lower proportion of transplant patients who withdrew from treatment or who had an uncertain/undetermined cause of death. Statistically, there were significant differences between the dialysis and transplant groups for each category except cerebrovascular disease and infection.

	Dialysis No.	**Dialysis %**	**Transplt No.**	**Transplt %**	**Total No.**	**Total %**	***p* value**
Cardiovascular	1511	30.7	480	36.6	1991	31.9	<0.001
Cerebrovascular accident	398	8.1	87	6.6	485	7.8	0.089
ERF treatment stopped	616	12.5	43	3.3	659	10.6	<0.001
Infection	865	17.6	243	18.5	1108	17.8	0.424
Malignancy	324	6.6	149	11.4	473	7.6	<0.001
Others	456	9.3	178	13.6	634	10.2	<0.001
Uncertain or not determined	757	15.4	130	9.9	887	14.2	<0.001
Total	4927	100	1310	100	6237	100	

Table 15.1: Cause of death by treatment modality
ERF, established renal failure.

	Dial <55		Dial 55+		Total trans		Dialysis <65		Dialysis ≥65		Total Dialysis	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cardiovascular	220	37.2	260	36.2	480	36.6	588	33.3	923	29.2	1511	30.7
Cerebrovascular accident	41	6.9	46	6.4	87	6.6	159	9.0	239	7.6	398	8.1
ERF treatment stopped	19	3.2	24	3.3	43	3.3	116	6.6	500	15.8	616	12.5
Infection	116	19.6	127	17.7	243	18.5	318	18.0	547	17.3	865	17.6
Malignancy	50	8.4	99	13.8	149	11.4	123	7.0	201	6.4	324	6.6
Others	90	15.2	88	12.3	178	13.6	190	10.8	266	8.4	456	9.3
Uncertain or not determined	56	9.5	74	10.3	130	9.9	273	15.4	484	15.3	757	15.4
Total	592	100	718	100	1310	100	1767	100	3160	100	4927	100

Table 15.2: Cause of death by modality and age

Incident patients

The data for incident patients were analysed for cause of death within the first 90 days and for the period 1 year after 90 days. These subsets (early deaths) were defined to allow a meaningful comparison with the USA and other international registries, where data on RRT are not collected for the first 90 days. International data were retrieved from the respective national registries and the European Renal Association (ERA).[1–6] Causes of death were also analysed for those who had survived at least 3 years, and at least 5 years, on RRT (late deaths).

Analysis of deaths in the first 90 days

For the incident cohort, there were a total of 1030 deaths within the first 90 days (Table 15.3), of which 564 (55%) had a recorded cause. The single largest cause of death was cardiovascular disease (31.9%). Proportionately, the causes of death were similar to those in the prevalent population, except fewer died of 'other' causes (6.6% versus 12.1% respectively).

	All Deaths	All % of those with data	<65 Deaths	<65 % of those with data	65+ Deaths	65+ % of those with data
Cardiovascular	180	31.9	58	39.5	122	29.3
Cerebrovascular accident	39	6.9	9	6.1	30	7.2
ERF treatment stopped	67	11.9	7	4.8	60	14.4
Infection	106	18.8	18	12.2	88	21.1
Malignancy	45	8.0	15	10.2	30	7.2
Others	37	6.6	13	8.8	24	5.8
Uncertain or not determined	90	16.0	27	18.4	63	15.1
Total with cause of death	564		147		417	
No cause of death sent	466		104		362	

Table 15.3: Cause of death by age in incident patients in the first 90 days

Primary diagnosis	Exposure years	Deaths	Rate per 1000 pt years exposed	Lower 95% CI	Upper 95%CI	Ref with GN
Amyloid	41.3	27	654.2	407.4	900.9	6.20
Cystic/polycystic	259.3	9	34.7	12.0	57.4	0.33
Diabetes	507.8	122	240.2	197.6	282.9	2.28
Glomerulonephritis	398.3	42	105.5	73.6	137.4	1.00
Interstitial	50.7	8	157.9	48.5	267.2	1.50
Malignancy	55.1	63	1142.8	860.6	1425.0	10.84
Pyelonephritis	372.5	49	131.5	94.7	168.4	1.25
Renal vascular disease	374.6	151	403.1	338.8	467.3	3.82
Other	572.4	317	553.8	492.8	614.8	5.25
Uncertain	734.2	242	329.6	288.1	371.2	3.13
Unknown	0.2	0	0	0	0	0
Total	3366.5	1030	306.0	287.2726	324.6	2.90

Table 15.4: Death rate, by primary diagnosis, in incident patients in the first 90 days
Ref with GN, referenced against glomerulonephritis.

When analysed by age group, there was no difference in the rate of recording a cause of death for those patients aged less than 65 years and those aged 65 and over. Cardiac death remained the most common cause in both age groups, although proportionally more of the younger patients died of cardiovascular causes (39.5% versus 29.3%) and more of the older patients died of infection-related illnesses (21.1% versus 12.2%) and treatment withdrawal (14.4% versus 4.8%).

The average death rate for all incident patients within the first 90 days was 306 per 1000 patient years exposed (pt yrs exp) (Table 15.5).

Age group	Exp years	Deaths	Rate per 1000 exposed years
15–19	40.4	0	0.0
20–24	126.4	2	15.8
25–29	140.9	3	21.3
30–34	170.9	4	23.4
35–39	202.8	8	39.5
40–44	206.7	12	58.1
45–49	246.8	23	93.2
50–54	280.4	37	131.9
55–59	315.9	60	189.9
60–64	341.4	102	298.7
65–69	395.8	187	472.5
70–74	411.9	226	548.7
75–79	318.4	208	653.3
80–84	128.3	113	881.0
85–89	35.0	42	1198.3
90+	4.4	3	683.1
Total	3366.5	1030	306.0

Age group	Exp years	Deaths	Rate per 1000 exposed years
20–44	847.7	29	34.2
45–64	1184.6	222	187.4
65+	1293.8	779	602.1

Table 15.5: Death rate, by age, in incident patients in the first 90 days

When the effect of primary diagnosis was analysed, patients with cystic/polycystic disease had the best outcome, with a rate of death of 34.7/1000 pt yrs exp (Table 15.4) and malignancy the poorest (1142.8/1000 pt yrs exp). When using glomerulonephritis (GN) as a reference point, cystic/polycystic patients had a significantly lower death rate and pyelonephritis a similar rate, whereas all other primary diseases had a significantly higher rate of death. These findings were similar to those in the subsequent analysis of the prevalent cohort (see Table 15.15 below). The effect of malignancy was substantially greater in this cohort than in the prevalent group (10.8 versus 3.3), as too was amyloidosis (6.2 versus 1.8). Women had a non-significant lower rate of death overall (279 versus 323; Table 15.6).

	Exp years	Deaths	Rate/1000
Male	2074	669	323
Female	1293	361	279
Total	3367	1030	306

Table 15.6: Death rate, by gender, in incident patients in the first 90 days

It is important to note the relevance of accuracy in the enrolment of patients for potentially long-term renal replacement therapy in this 90 day incident cohort. Evidence suggests variation in the criteria applied in different units, and some cases are bound to be subject to interpretation. Uncertainties of classification will inevitably bias the outcome data and are unlikely to be fully resolved in current Registry practice.

Analysis of deaths in the first year after 90 days

There were 1857 deaths in the 1 year after the 90 days analysis (Table 15.7), with a recorded cause in 1023 (55%) patients. The overall rate of death was 188/1000 pt yrs exp (Table 15.9), contrasting with 306/1000 pt yrs exp within the first 90 days (see Table 15.5 above); these figures increased with increasing patient age.

Table 15.7 shows that cardiac disease, accounting for 29% of deaths, remained the most common cause of death, although it accounted for a smaller percentage of deaths in those aged less than 65 years than occurred for the 90 day cohort (32% versus 40%). Similar to the 90 day analysis, treatment withdrawal was more common in those aged over 65 years (18.2% versus 9.7%, $p<0.01$), although, as a group, withdrawal was slightly more common in the 1 year after 90 days group (15.5% versus 11.9% respectively). Infection-related deaths were similar in both age groups (16.6% versus 18.3%), and this contrasts with the first 90 day period, in which infections accounted for a lower proportion of deaths in patients aged less than 65 years (12% versus 21%).

Cause of death	All Deaths	All % of those with data	<65 Deaths	<65 % of those with data	65+ Deaths	65+ % of those with data
Cardiovascular	298	29.1	102	32.0	196	27.8
Cerebrovascular accident	79	7.7	25	7.8	54	7.7
ESRF treatment stopped	159	15.5	31	9.7	128	18.2
Infection	182	17.8	53	16.6	129	18.3
Malignancy	94	9.2	29	9.1	65	9.2
Others	76	7.4	30	9.4	46	6.5
Uncertain or not determined	135	13.2	49	15.4	86	12.2
Total with cause of death	1023		319		704	
No cause of death sent	834		224		610	

Table 15.7: Cause of death, by age, in incident patients at 1 year + 90 days

	Exp years	Deaths	Rate/1000	Lower 95% CI	Upper 95% CI	Compare to GN
Amyloid	113.6	43	378.5	265.4	491.7	5.69
Cystic/polycystic	834.3	31	37.2	24.1	50.2	0.56
Diabetes	1447.4	310	214.2	190.3	238.0	3.22
Glomerulonephritis	1262.0	84	66.6	52.3	80.8	1
Interstitial	140.2	24	171.2	102.7	239.7	2.57
Malignancy	111.6	116	1039.8	850.6	1229.0	15.62
Pyelonephritis	1190.3	112	94.1	76.7	111.5	1.41
Renal vascular disease	1040.2	239	229.8	200.6	258.9	3.45
Other	1534.9	474	308.8	281.0	336.6	4.64
Uncertain	2187.5	424	193.8	175.4	212.3	2.91
Total	9861.8	1857	188.3	179.7	196.9	2.83

Table 15.8: Death rate, by primary diagnosis, in incident patients at 1 year + 90 days

Age group	Exposure years	Deaths	Rate per 1000 exp years
15–19	144.9	1	6.9
20–24	448.6	7	15.6
25–29	492.4	9	18.3
30–34	565.7	25	44.2
35–39	664.3	28	42.1
40–44	671.8	29	43.2
45–49	797.1	53	66.5
50–54	867.0	72	83.0
55–59	975.9	122	125.0
60–64	979.7	197	201.1
65–69	1096.9	318	289.9
70–74	1061.8	412	388.0
75–79	756.1	345	456.3
80–84	270.0	176	651.7
85–89	62.7	54	861.3
90+	7.0	9	1293.8
Total	9861.8	1857	188.3

Age group	Exp years	Deaths	Rate per 1000 exp years
20–44	2842.8	98.0	34.5
45–64	3619.7	444.0	122.7
65+	3254.5	1314.0	403.8

Table 15.9: Death rate, by age, in incident patients at 1 year + 90 days

In the analysis of the effect of primary diagnosis, the results were similar to those for incident patient deaths at 90 days (Table 15.8). Ratios using GN as a reference were similar in both incident cohorts, but it should be noted, although not significant, that men had a lower rate of death than women (185 versus 192/1000 pt yrs exp; Table 15.10).

	Exp years	Deaths	Rate/1000
Male	6058	1125	185
Female	3803	732	192
Total	9861	1857	188

Table 15.10: Death rate, by gender, in incident patients at 1 year + 90 days

Comparing the first 90, and 1 year after 90, days, rates of death were identical in the 20–44-year age band (34/1000 pat yrs exp), but rates were higher in the first 90 days than 1 year after 90 days in the age bands 45–64 years (187 versus 123/1000 pat yrs exp) and 65+ years (602 versus 404/1000 pat yrs exp). Overall, the rate of death was lower in the 1 year after 90 days (188/1000 pat yrs exp), compared with the first 90 days (306/1000 pat yrs exp).

Table 15.11 analysed cause of death by time on RRT (less than 3 years and longer than 3 years) with age under 65 or over 65, and similarly Table 15.12 in relation to 5 years. Cardiac death was again the most common cause across age groups and independent of time on RRT. Withdrawal of treatment as a proportion of deaths fell with increasing time on RRT; this was most pronounced in those patients aged 65 years and over (12%, 16%, 13%, 8% at 90 days, 1 year after 90 day, 3 years and 5 years respectively).

	All ages	<65		65+	
Cause of death	**3+ yrs on RRT**	**3+ yrs on RRT**	**<3 yrs on RRT**	**3+ yrs on RRT**	**<3 yrs on RRT**
Cardiovascular	390 (29.8%)	886 (32.9%)	469 (34.1%)	496 (35.8%)	636 (29.4%)
Cerebrovascular accident	93 (7.1%)	208 (7.7%)	111 (8.1%)	115 (8.3%)	166 (7.7%)
ERF treatment stopped	175 (13.4%)	236 (8.8%)	83 (6.0%)	61 (4.4%)	340 (15.7%)
Infection	233 (17.8%)	477 (17.7%)	255 (18.5%0	244 (17.6%)	376 (17.4%)
Malignancy	90 (6.9%)	203 (7.5%)	107 (7.8%)	113 (8.2%)	163 (7.5%)
Others	123 (9.4%)	303 (11.2%)	154 (11.2%)	180 (13.0%)	177 (8.2%)
Uncertain or not determined	205 (15.7%)	381 (14.1%)	198 (14.4%)	176 (12.7%)	308 (14.2%)
Total	1309	2694	1377	1385	2166

Table 15.11: Cause of death, by time, on RRT at 3 years

When comparing rates of death between incident and prevalent patients, causes of death were similar (Tables 15.4 and 15.15, and see Table 15.8 above), although age had an effect. Proportionately, there were higher rates of stroke, treatment withdrawal and infection in prevalent patients aged less than 65 when compared with incident patients who died in the first 90 days, but not those dying 1 year after 90 days.

	All ages	<65		65+	
Cause of death	**5+ yrs on RRT**	**<5 yrs on RRT**	**5+ yrs on RRT**	**<5 yrs on RRT**	**5+ yrs on RRT**
Cardiovascular	572 (32.7%)	607 (34.0%)	358 (36.6%)	812 (30.0%	214 (27.8%0
Cerebrovascular accident	136 (7.8%)	146 (8.2%)	80 (8.2%)	203 (7.5%)	56 (7.3%)
ESF treatment stopped	133 (7.6%)	105 (5.9%)	39 (4.0%)	421 (15.6%)	94 (12.2%)
Infection	297 (17.0%)	338 (19.0%)	161 (16.4%)	473 (17.5%)	136 (17.7%)
Malignancy	143 (8.2%)	136 (7.6%)	84 (8.6%)	194 (7.2%)	59 (7.7%)
Others	182 (10.4%)	221 (12.4%)	113 (11.5%)	231 (8.5%)	69 (9.0%)
Uncertain or not determined	285 (16.3%)	230 (12.9%)	144 (14.7%)	372 (13.7%)	141 (18.3%)
Total	1748	1783	979	2706	769

Table 15.12: Cause of death, by time, on RRT at 5 years

Prevalent patients and comparison with the general population

Cause of death	**All No. of Deaths**	**All % of those with data**	**<65 Deaths**	**<65 % of those with data**	**65+ Deaths**	**65+ % of those with data**
Cardiovascular	157	31.2	57	33.7	100	29.9
Cerebrovascular accident	40	8.0	17	10.1	23	6.9
ERF treatment stopped	71	14.1	15	8.9	56	16.8
Infection	86	17.1	28	16.6	58	17.4
Malignancy	31	6.2	13	7.7	18	5.4
Others	61	12.1	24	14.2	37	11.1
Uncertain or not determined	57	11.3	15	8.9	42	12.6
Total with cause of death	503		169		334	
No cause of death sent	547		151		396	

Table 15.13: Cause of death in prevalent patients, by age

There were a total of 1050 deaths in this cohort, 503 (48%) of which had a recorded cause. In total, 66% of deaths occurred in those patients aged over 65 years. Cardiac death was the most common cause (31.2%) irrespective of age group under or over 65 years (Table 15.13). Treatment withdrawal was significantly (p<0.05) more common in those aged over 65 than those under 65 (16.8% versus 8.9% respectively).

The rates of death by primary diagnosis (Table 15.14) and age (Tables 15.16) were calculated; not unexpectedly, death rate increased with increasing age, the highest rate of death being seen in those with underlying malignancy (497/1000 pat yrs exp). The three lowest rates were seen in those with either cystic/polycystic disease (117/1000 pat yrs exp), GN (151/1000 pat yrs exp) or pyelonephritis (159/1000 pat yrs exp). A comparison of primary diagnoses with GN as the reference (Table 15.15) showed that all other primary diseases had a significantly different rate of death except pyelonephritis. Cystic/polycystic disease had a better, and pyelonephritis a similar, outcome related to GN, whereas other conditions had a significantly poorer one. Gender differences were not significant, with rates of death 214/1000 pat yrs exp in males compared with 198 in females (Table 15.14).

EDTA group	Exposure years	Deaths	Rate/1000 yrs exp
Amyloid	48.0	13	271.0
Cystic/polycystic	375.0	44	117.3
Diabetes	812.5	223	274.5
Glomerulonephritis	548.9	83	151.2
Interstitial	89.1	26	291.9
Malignancy	50.3	25	496.7
Pyelonephritis	546.0	87	159.3
Renal vascular disease	587.0	128	218.1
Other	820.3	166	202.4
Uncertain	1185.6	255	215.1
Total	5062.7	1050	207.4
Male	3027.9	648	214.0
Female	2034.8	402	197.6

Table 15.14: Rate of death, by gender and primary diagnosis, in prevalent patients

EDTA group	Exp years	Deaths	Rate/1000	Lower 95% CI	Upper 95% CI	Compare with GN
Amyloid	48.0	13	271.0	123.68	418.32	1.79
Cystic/polycystic	375.0	44	117.3	82.65	151.98	0.78
Diabetes	812.5	223	274.5	238.44	310.48	1.82
Glomerulonephritis	548.9	83	151.2	118.67	183.73	1
Interstitial	89.1	26	291.9	179.69	404.09	1.93
Malignancy	50.3	25	496.7	302.00	691.42	3.29
Pyelonephritis	546.0	87	159.3	125.86	192.83	1.05
Renal vascular disease	587.0	128	218.1	180.29	255.85	1.44
Other	820.3	166	202.4	171.58	233.15	1.34
Uncertain	1185.6	255	215.1	188.68	241.48	1.42
Total	5062.7	1050	207.4	194.85	219.94	1.37

Table 15.15: Rate of death in prevalent patients, by primary diagnoses

Table 15.16 uses data from the Office for National Statistics (ONS) and shows the population by age band for England & Wales, and the number of deaths per thousand in the general population. The death rates of patients on RRT were calculated and a figure derived for the observed number of deaths on RRT. This was divided by the expected number of deaths calculated for the general population to provide the relative risk (RR) of dying given

underlying established renal failure (ERF), compared with another individual of the same age group without ERF in England & Wales. Results showed that although the death rate increases with increasing age, the risk of death compared with the general population without ERF is greatest in the younger age bands (Table 15.16 and Figure 15.1). The RR of dying for 20–24-year-olds on RRT was 121.4 compared with 5.1 in the 80–84-year-olds.

Age	E&W Pop mid-98 (000)	E&W deaths	E&W /1000 pop	Ren Reg exposed years	Expected	RenReg deaths	RenReg deaths per 1000	Obs/exp
20–24	3084.2	1832	0.6	83.2	0.0	6	72.1	121.4
25–29	3883.4	2364	0.6	140.2	0.1	6	42.8	70.3
30–34	4294	3187	0.7	163.4	0.1	19	116.3	156.7
35–39	4035.4	4345	1.1	247.7	0.3	19	76.7	71.3
40–44	3479.8	5643	1.6	276.7	0.4	37	133.7	82.5
45–49	3403.8	8331	2.4	355.7	0.9	41	115.3	47.1
50–54	3500.1	14132	4.0	472.2	1.9	64	135.5	33.6
55–59	2709.4	18481	6.8	553.8	3.8	96	173.3	25.4
60–64	2489.8	27244	10.9	610.2	6.7	130	213.0	19.5
65–69	2314.6	40735	17.6	747.4	13.2	174	232.8	13.2
70–74	2085.8	62384	29.9	694.4	20.8	210	302.4	10.1
75–79	1781.3	88977	50.0	488.6	24.4	168	343.8	6.9
80–84	1089.6	88123	80.9	156.0	12.6	64	410.2	5.1
85–89	669	89474	133.7	34.6	4.6	13	375.3	2.8
90+	347.7	76482	220.0	3.6	0.8	3	834.6	3.8
Total	42386.5	533035	12.6	5027.7	90.6	1050	208.8	11.6

Table 15.16: Death rate, by age, for prevalent patients: comparisons with the general population

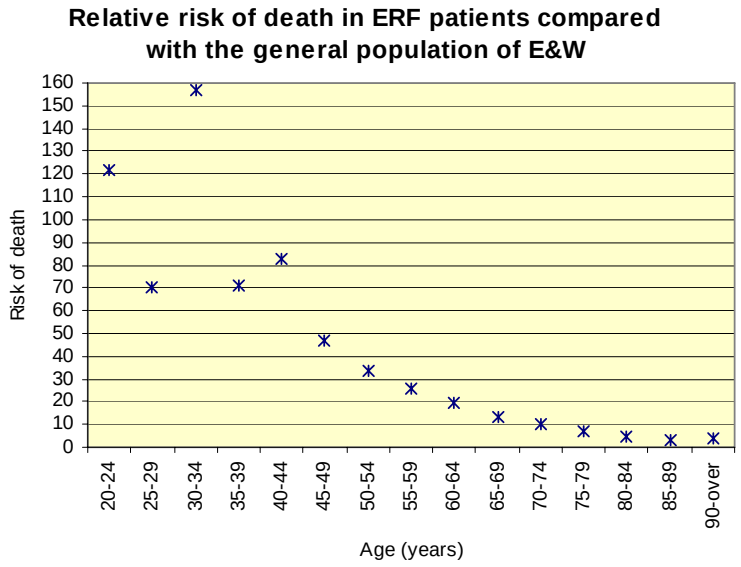

Figure 15.1: Relative risk of death in ERF patients

We also compared causes of death in the ERF population with that in the general population of England & Wales as supplied by the ONS (Table 15.17). In the general population, the three most common causes of death were classified as 'other' (27.8%), malignancy (25.2%) and cardiovascular disease (24%). Very few people had a recorded cause of death of diabetes, or one of its associated complications, although this probably reflects the stringency applied to death certification. When compared with the ERF population, proportionately more renal patients died of a cardiac cause (31.2% versus 24%), reflecting a 23% or 1.3-fold increased

risk of death in these patients. Similarly, infection was more common as a cause of death in renal patients (17.1% versus 11.5%) reflecting a 33% or 1.5-fold increase in risk. Maybe as a consequence, or as a reflection of the selection of patients taken on for RRT, the risk of malignancy in the ERF group was much lower than that of the general population (6.2% versus 25.2%, a 75% or fourfold decreased risk).

	Sex	No. 15–64	No. 65+	No. Total	% 15–64	% 65+	% Total
Cardiovascular	All	16,475	111,559	128,034	19.0	25.0	24.0
Cerebrovascular accident	All	3,968	48,491	52,459	4.6	10.9	9.8
Diabetes	All	860	4,902	5,762	1.0	1.1	1.1
Infection	All	4,187	57,215	61,402	4.8	12.8	11.5
Malignancy	All	32,745	101,495	134,240	37.7	22.7	25.2
Other	All	26,445	121,837	148,282	30.4	27.3	27.8
Uncertain or not determined	All	2,180	676	2,856	2.5	0.2	0.5
Total	All	86,860	446,175	533,035	100.0	100.0	100.0

Table 15.17: Population deaths, by sex and age

Age	E&W Pop mid-98 (000)	E&W Deaths	E&W/1000 pop	Ren Reg exp years	Ren Reg deaths	UK RR deaths per 1000	USA deaths per 1000	RR/USA
20–44	18,515.6	13,029.0	0.7	911.1	87	95.5	56.1	1.70
45–64	13,093.1	46,587.0	3.6	1,991.9	331	166.2	136.3	1.22
65+	10,430.1	396,937.0	38.1	2,124.7	632	297.5	340.4	0.87
Total	42,038.8	456,553.0	10.9	5,027.7	1050	208.8	179.3	1.16

Table 15.18: Death rate, by age, for prevalent patients and comparison with the USA

In Table 15.18, UK prevalent patients in the younger age group had a higher rate of death than those in the USA. The UK deaths, unlike the USA data, include those patients who died within the first 90 days, and this may account for the higher rate of death. UK patients aged over 65 years have a lower rate of death than in the USA, which is probably related to the high take-on rate in the USA, with a higher rate of comorbidity in these patients.

Effect of comorbidity

The influence of comorbidity on death was assessed in the incident population of RRT patients. The number of patients with both comorbidity at the start of RRT and cause of death recorded were currently too small to analyse the effect of these factors on death at 90 days and 1 year after 90 days. The analysis includes all incident patients with complete records who died within 3 years of starting RRT. There were 640 deaths in the patient group with completed comorbidity. Of these, 365 patients (57%) had a cause of death recorded, a similar level of completion to both the incident and prevalent groups.

Comparison of cardiovascular and peripheral vascular comorbidity

Because of the limited data, comorbidity was grouped into:

1. cardiovascular disease;
2. generalised (mainly peripheral) vascular disease;
3. either of these groups;
4. patients recorded as having no comorbidity present.

In Table 15.19, of those patients recorded as having cardiovascular disease at the time of starting RRT (n=129), 52.7% (n=68) died from a cardiac cause. In comparison, of patients recorded as having no cardiovascular disease (n=236), only 17.8% (n=42) died from cardiac causes, and their causes of death were more widely distributed. The presence of generalised vascular disease at the start of RRT (Table 15.20) did not affect the rate of cardiac death when compared with the previous analysis of the complete incident population.

	No cardiovasc	No %	Yes cardiovasc	Yes %	Total No.	Total %
Cardiovascular	42	17.8	68	52.7	110	30.1
Cerebrovascular accident	19	8.1	8	6.2	27	7.4
ERF treatment stopped	54	22.9	16	22.4	70	19.2
Infection	43	18.2	15	11.6	58	15.9
Malignancy	28	11.9	6	4.7	34	9.3
Others	28	11.9	6	4.7	34	9.3
Uncertain or not determined	15	6.4	9	7.0	24	6.6
Total	236		129		365	

Table 15.19: Cardiovascular comorbidity and cause of death

	No Vasc dis	No %	Yes Vasc dis	Yes %	Total No.	Total %
Cardiovascular	64	27.9	46	33.8	110	30.1
Cerebrovascular accident	16	7.0	11	8.1	27	7.4
ERF treatment stopped	41	17.9	29	21.3	70	19.2
Infection	40	17.5	18	13.2	58	15.9
Malignancy	27	11.8	7	5.1	34	9.3
Others	29	12.7	13	9.6	42	11.5
Uncertain or not determined	12	5.2	12	8.8	24	6.6
Total	229		136		365	

Table 15.20: Generalised vascular comorbidity and cause of death

	None	No %	Any	Yes %	Total No.	Total %
Cardiovascular	27	16.4	83	41.5	110	30.1
Cerebrovascular accident	13	7.9	14	7.0	27	7.4
ERF treatment stopped	34	20.6	36	18.0	70	19.2
Infection	33	20.0	25	12.5	58	15.9
Malignancy	24	14.5	10	5.0	34	9.3
Others	24	14.5	18	9.0	42	11.5
Uncertain or not determined	10	6.1	14	7.0	24	6.6
Total	165		200		365	

Table 15.21: Cardiovascular or peripheral vascular comorbidity and cause of death

In those patients without cardiac or circulatory disease on starting RRT (Table 15.21), treatment withdrawal was the most common cause of death (20.6%), although causes were more evenly distributed across all the categories.

Diabetes and cause of death

Patients with type I and II diabetes were analysed as a single group. Patients were included in this analysis if they had diabetes as the primary diagnosis for the cause of their renal disease or if it was recorded as a comorbidity response. Prevalent and incident patients were assessed separately.

Incident patients with diabetes

In the incident patients, diabetics had a lower rate of death in the first 90 days than non-diabetics (Table 15.22), probably because of their younger age (58 versus 60 years). Of the 1030 deaths in the first 90 days, 12% occurred in patients with diabetes. Table 15.23 shows that these diabetic patients had a significantly greater rate of cardiac death than the non-diabetics (53% versus 29%, $p<0.01$).

	Exp years	Deaths	Rate/1000	Lower 95% CI	Upper 95% CI
Non-diabetics	2858.63	908	317.6	296.97	338.30
Diabetics	507.847	122	240.2	197.60	282.86

Table 15.22: Death rate, by diabetes, in incident patients at 90 days

	Non-diabetic No.	Non-diabetic %	Diabetic No.	Diabetic %	Total	%	*p*	Adjust *p*
Cardiovascular	139	28.5	41	53.2	180	31.9	0.00	<0.01
Cerebrovascular accident	35	7.2	4	5.2	39	6.9	0.52	NS
ERF treatment stopped	62	12.7	5	6.5	67	11.9	0.12	NS
Infection	98	20.1	8	10.4	106	18.8	0.04	NS
Malignancy	45	9.2	0	0	45	8.0	0.06	NS
Others	32	6.6	5	6.5	37	6.6	0.98	NS
Uncertain or not determined	76	15.6	14	18.2	90	16.0	0.57	NS
Total	487	100	122	100	609	100		
No data	421		45		466			

Table 15.23: Cause of death, by diabetes, in incident patients at 90 days

In the 1 year after 90 days period (Table 15.24), the death rate was higher in diabetics than non-diabetics (214 versus 184/1000 pat yrs exp respectively). Again, cardiac death was significantly more common in the diabetic patients (42% versus 26%, $p<0.01$; Table 15.25).

	Exp years	Deaths	Rate/1000	Lower 95% CI	Upper 95% CI
Non-diabetics	8414.45	1547	183.9	174.69	193.01
Diabetics	1447.36	310	214.1	190.34	238.03

Table 15.24: Death rate, by diabetes, in incident patients at 1 year after 90 days

Cause of death	Non-diabetic No.	Non-diabetic %	Diabetic No.	Diabetic %	Total	%	*p*	Adjust *p*
Cardiovascular	221	26.4	77	41.6	298	29.1	<0.01	<0.01
Cerebrovascular accident	65	7.8	14	7.6	79	7.7	0.93	NS
ERF treatment stopped	130	15.5	29	15.7	159	15.5	0.96	NS
Infection	152	18.1	30	16.2	182	17.8	0.54	NS
Malignancy	91	10.9	3	1.6	94	9.2	<0.01	<0.01
Others	69	8.2	7	3.8	76	7.4	0.04	NS
Uncertain or not determined	110	13.1	25	13.5	135	13.2	0.89	NS
Total	1547	100	310	100	1857	100		
No cause of death sent	709		125		834			

Table 15.25: Cause of death, by diabetes, in incident patients at 1 year after 90 days

Prevalent patients with diabetes

Of the 1050 prevalent patients in Table 15.26, 223 (21%) were diabetic, and their rate of death was significantly higher than that of non-diabetics (275 versus 195/1000 pt yrs exp, $p<0.01$). Of these diabetics, 112 (50%) had a cause of death recorded.

In analysing those with data (Table 15.27), diabetics had a proportionately higher incidence of cardiac deaths compared with non-diabetics (41% versus 28%); this did not reach statistical significance. They did, however, have significantly more deaths from cerebrovascular accident ($p<0.05$).

	Exp Years	Deaths	Rate/1000	Lower 95% CI	Upper 95% CI
Non-diabetics	4250.2	827	194.6	181.32	207.84
Diabetics	812.5	223	274.5	238.44	310.48

Table 15.26: Death rate for prevalent diabetic patients

Cause of death	Non-diabetic	Non-diabetic %	Diabetic n	Diabetic %	Total	%	*p*	Adjust *p*
Cardiovascular	111	28.3	46	41.4	157	31.2	0.01	NS
Cerebrovascular accident	24	6.1	16	14.4	40	8.0	<0.01	<0.05
ERF treatment stopped	60	15.3	11	9.9	71	14.1	0.15	NS
Infection	63	16.1	23	20.7	86	17.1	0.25	NS
Malignancy	27	6.9	4	3.6	31	6.2	0.20	NS
Others	57	14.5	4	3.6	61	12.1	<0.01	<0.05
Uncertain or not determined	50	12.8	7	6.3	57	11.3	0.06	NS
Total	827	100	223	100	1050	100		
No cause of death sent	435		112		547			

Table 15.27: Effect of diabetes on cause of death in prevalent patients

International comparisons

Comparisons were possible with data from European, North American and Australasian Registries.

USA

Using data from the US Renal Data System (USRDS) 2001 annual report,[4] rates of death for UK patients were compared by age band (see Table 15.18 above). Rates of death in the UK were significantly higher than in USA in the younger and middle-aged bands but significantly lower in the 65+ age group ($p<0.01$). This difference in the elderly may be due to the fact that, in the USA, patients with very high rates of comorbidity (but who survive more than 90 days) all start RRT, whereas in England & Wales, take-on rates are much lower and there is selection bias. The USA data omit deaths in the first 90 days, which may be part of the reason for the apparently higher mortality in the UK in the younger age groups.

In the USRDS report, causes of death categories were divided into many subgroups within the cardiovascular causes. With the larger patient number, deaths were split by myocardial infarction, cardiac arrest, cause unknown and cardiac other. The data showed that cardiovascular disease was the most common cause of death across all RRT modalities, although most transplant patients died of unknown cause (31.7 per 1000 patient years exposed).

Canada

The 2001 Canadian report, based on data from RRT patients in 1999,[5] provided details on 2652 deaths in 26,209 prevalent patients (10.1%). Cardiovascular disease remained the most common cause of death (38.2%), although the proportion was higher than in UK patients (31.7%). The next most common cause was 'social' (15.4%), and although this category included suicide as well as treatment withdrawal, the rate was comparable to that recorded for the UK (14.1%). Infection was believed responsible for only 9.7% of deaths, much less common than the 18.3% for the UK cohort.

Norway

The registries of Norway and Finland both quoted cause of death by proportions, and their categories differed slightly from those used in the UK. Of 278 deaths in prevalent patients on RRT in 2001 in Norway,[3] 11% died from treatment withdrawal, 33% from cardiac causes, 23% from infection, 20% from vascular disease and 12% from malignancy. Results are comparable with those from the UK for cardiac disease and treatment withdrawal, but proportionately more Norwegian than UK patients died from infection and malignancy.

Finland

In Finland, cardiac and cerebrovascular diseases were combined as a cause of death, this category accounting for 48% of all deaths on RRT.[2] The proportion of deaths from infective causes was similar to the UK Registry figures (18% versus 17.1%), but other diagnostic categories were not suitable for direct comparison.

Australia and New Zealand

In the combined Australia and New Zealand Registry report,[6] death rate was analysed by proportion and per 100 patient years at risk. This included all patients treated during the year 2000. Within Australia, 12% of dialysis patients died (15.7 deaths/100 pt yrs exp), compared with 2.9% of those with a functioning transplant (3.2 deaths/100 pt yrs exp). The rates in New Zealand differed, with 19.2 deaths per 100 patient years for dialysis and 2.5 for transplant recipients. In both dialysis patients and transplant recipients, cardiac events were the most common cause of death (46% versus 29% in Australia, 43% versus 24% in New Zealand). Within the dialysis cohort, treatment withdrawal accounted for 21% and 22% of deaths respectively in Australia and New Zealand, the majority of these cases having underlying diabetes. The cardiac death rate in Australia was higher than that in England & Wales (46% versus 32%). The treatment withdrawal rate was also substantially higher in Australia (48% of dialysis patients) and New Zealand (18%), compared with England & Wales (14%), whereas the infection rate was lower in Australia (12% in dialysis patients).

European ERA/EDTA Registry

The ERA report for 2000 included data from Austria, Belgium, Finland, France, the Netherlands, Norway and Scotland. The ERA has analysed data on causes of death from the years 1991–99.[1,7] During this period, there were 19,851 deaths, and the distribution of causes of death did not change. The most common cause of death was cardiac, accounting for the deaths of 36% of dialysis patients and 35% of transplant patients (Figure 15.2), followed by infection and malignancy in decreasing order of frequency. All these data were comparable with the results from the UK.

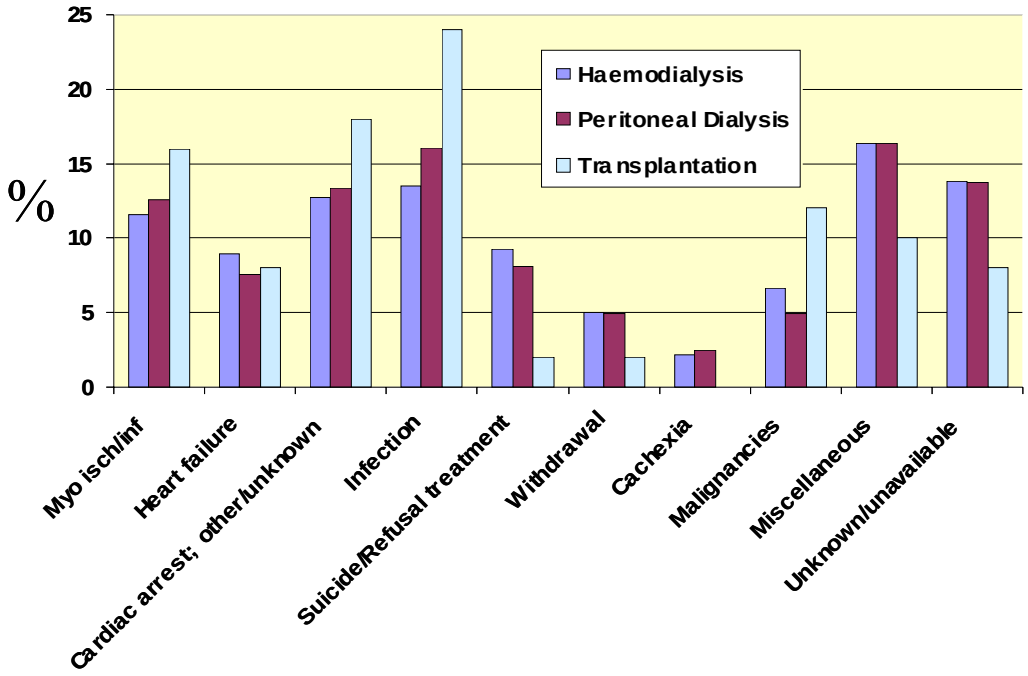

Figure 15.2: ERA-EDTA causes of death

Conclusion

These data confirmed what has been shown by other national Renal Registries, that cardiovascular disease is the most common cause of death in patients on RRT and that this is most evident in the diabetic population. In patients aged 65 years and over, there was also a high frequency of deaths caused by treatment withdrawal.

When compared with the general population of England & Wales, cardiac deaths were proportionately more common in patients on RRT – a 23% increase. This may be a reflection of the comorbidity present at the start of renal replacement, the ageing RRT population and the effect of ERF itself. In those patients with comorbidity data and a recorded cause of death, 50% of patients with cardiac disease on starting RRT died of a cardiac cause. Diabetics were more likely to die from cardiac disease but also had an increased risk of death from cerebrovascular disease. Causes of death were similar among prevalent and incident patients irrespective of time on RRT.

Infection-related deaths were more common in the ERF cohort than in the general population (17.1% versus 11.5%), representing a 33% increase. These deaths will be related to a combination of factors, including vascular access, peritonitis, atypical infections, and also the effect of immunosuppressive regimes.

As expected, death rate increased with increasing age, and although women tended to have a better outcome, this did not reach statistical significance. When looking at all-cause death by age, 25–29-year-olds with ERF had a 156-fold higher risk of death compared with the general population. This contrasts with a 5.1-fold increase in the 80–84-year-old patients on RRT.

The underlying primary renal diagnosis had a significant effect on death rate, irrespective of age. Those patients with malignancy, not surprisingly, had the poorest outcomes, whereas cystic/polycystic patients had the best. Patients with pyelonephritis and GN also showed an improved outcome compared with those with other diseases.

In general, the UK data compared favourably with those of other Registries. When compared with USRDS data, younger patients in the UK had a significantly higher rate of death. This may be in part explained by differences in timing of the data collection (the 90 day rule) and ethnic mix. UK data include all patients on RRT from day 0, whereas US figures exclude patients for the first 90 days of RRT because of collection issues and therefore miss a proportion of early deaths. Our data were unadjusted for ethnicity, yet the USRDS has shown that African-Caribbean males on dialysis have an improved survival. They had a death rate of 169.2/1000 pt yrs exp, compared with 288.4 in Whites.[4] Differences between ethnic groups were also seen in women, albeit to a lesser extent (204.0 versus 295.2/1000 pt yrs exp for African-Caribbean individuals and Whites respectively). In the over-65 age group, the UK had a better rate of survival, although this may be because of differences in case mix. A lack of uniformity in categorisation impedes the comparison of data from international sources.

With improved data returns, the Registry will be able to analyse further the effects of comorbidity and ethnicity on cause and rate of death. It will also be possible to analyse in greater detail particular diagnoses and their associated risk of death, and examine the effect of treatment modality.

EDTA causes of death and groupings

EDTA	Title	SubgroupB
0	Cause of death uncertain/not determined [0]	Uncertain or not determined
11	Myocardial ischaemia and infarction [11]	Heart
12	Hyperkalaemia [12]	Others
13	Haemorrhagic pericarditis [13]	Others
14	Other causes of cardiac failure [14]	Heart
15	Cardiac arrest/sudden death; other cause or unknown [15]	Heart
16	Hypertensive cardiac failure [16]	Heart
17	Hypokalaemia [17]	Others
18	Fluid overload/pulmonary oedema [18]	Heart
21	Pulmonary embolus [21]	Others
22	Cerebrovascular accident, other cause or unspecified [22]	Cerebrovascular accident
23	Gastrointestinal haemorrhage (digestive) [23]	Others
24	Haemorrhage from graft site [24]	Others
25	Haemorrhage from vascular access or dialysis circuit [25]	Others
26	Cerebral haemorrhage from ruptured vascular aneurysm (not code 22 or 23) [26]	Others
27	Haemorrhage from surgery (except digestive haemorrhage) [27]	Others
28	Other haemorrhage, other site and/or other cause [28]	Others

EDTA	Title	SubgroupB
0	Cause of death uncertain/not determined [0]	Uncertain or not determined
29	Mesenteric infarction [29]	Others
31	Pulmonary infection (bacterial) [31]	Infection
32	Pulmonary infection (viral) [32]	Infection
33	Pulmonary infection (fungal or protozoal; parasitic) [33]	Infection
34	Infections elsewhere except viral hepatitis	Infection
35	Septicaemia [35]	Infection
36	Tuberculosis (lung) [36]	Infection
37	Tuberculosis (elsewhere) [37]	Infection
38	Generalised viral infection [38]	Infection
39	Peritonitis (all causes except for peritoneal dialysis) [39]	Infection
41	Liver disease due to hepatitis B virus [41]	Others
42	Liver disease due to other viral hepatitis [42]	Others
43	Liver disease due to drug toxicity [43]	Others
44	Cirrhosis – not viral (alcoholic or other cause) [44]	Others
45	Cystic liver disease [45]	Others
46	Liver failure – cause unknown [46]	Others
51	Patient refused further treatment for ESRF [51]	ESRF treatment stopped
52	Suicide [52]	Others
53	ESRF treatment ceased for any other reason [53]	ESRF treatment stopped
54	ESRF treatment withdrawn for medical reasons [54]	ESRF treatment stopped
61	Uraemia caused by graft failure	ESRF treatment stopped
62	Pancreatitis [62]	Others
63	Bone marrow depression (aplasia) [63]	Others
64	Cachexia [64]	Others
66	Malignant disease in patient treated by immunosuppressive therapy [66]	Malignancy
67	Malignant disease: solid tumours except those of 66 [67]	Malignancy
68	Malignant disease: lymphoproliferative disorders (except 66) [68]	Malignancy
69	Dementia [69]	Others
70	Peritonitis (sclerosing, with peritoneal dialysis) [70]	Others
71	Perforation of peptic ulcer [71]	Others
72	Perforation of colon [72]	Others
73	Chronic obstructive pulmonary disease [73]	Others
81	Accident related to ESRF treatment (not 25) [81]	Others
82	Accident unrelated to ESRF treatment [82]	Others
99	Other identified cause of death [99]	Others
100	Peritonitis (bacterial, with peritoneal dialysis) [100]	Others
101	Peritonitis (fungal, with peritoneal dialysis) [101]	Others
102	Peritonitis (due to other cause, with peritoneal dialysis) [102]	Others

Table 15.28: Collation of EDTA codes for cause of death

References

1. ERA–EDTA Report

2. Finnish Registry for Kidney Diseases. Report 2000.

3. Annual Report 2001, Norwegian Renal Registry.

4. US Renal Data System. *USRDS 2001 Annual Data Report, Atlas of End Stage Renal Disease in the US National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases*. Bethseda, MD: NIH, 2001.

5. Canadian Institute for Health Information. *Register 2001 Report*. Vol 1: *Dialysis and Renal Transplantation. Canadian Organ Replacement Register*. Ottowa: Canadian Institute for Health Information, 2001.

6. Disney APS, Russ Graeme R. *Australia and New Zealand Dialysis and Transplant Registry Report 2001*. Adelaide: ANZDATA, 2001.

7. van Dijk Paul CW, et al. Renal replacement therapy in Europe: the results of a collaborative effort by the ERA–EDTA registry and six national or regional registries. *Nephrol Dial Transplant* 2001;16:1120–9.