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## Chapter 12

# Characteristics and outcomes of patients with systemic sclerosis (scleroderma) requiring renal replacement therapy in Europe: results from the ERA-EDTA Registry

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## Abstract

**Rational & Objective:** Data on outcomes of patients with ESRD secondary to systemic sclerosis (scleroderma) requiring RRT is limited. We examined the incidence and prevalence of ESRD due to scleroderma in Europe and the outcomes among these patients following initiation of RRT.

**Study Design:** Registry study of incidence and prevalence and a matched cohort study of clinical outcomes.

**Setting & Participants:** Patients represented in any of 19 renal registries that provided data to the ERA-EDTA Registry between 2002-2013.

**Predictor:** Scleroderma as the identified cause of ESRD.

**Outcomes:** Incidence and prevalence of ESRD from scleroderma. Recovery from RRT dependence, patient survival after ESRD and graft survival after kidney transplantation.

**Analytic approach:** Incidence and prevalence were calculated using population data from the European Union and standardised to population characteristics in 2005. Patient and graft survival were compared to two age- and sex-matched control groups without scleroderma: 1) diabetes mellitus (DM) as the cause of ESRD and 2) conditions other than DM as the cause of ESRD. Survival analyses were performed using Kaplan-Meier analysis and Cox regression.

**Results:** 342 patients with scleroderma (0.14% of all incident RRT patients) were included. Between 2002 and 2013, the range of adjusted annual incidence and prevalence rates of RRT for ESRD due to scleroderma were 0.11-0.26 and 0.73-0.95 per million population respectively. Recovery of independent renal function was greatest in the scleroderma group (7.6% vs. 0.7% in diabetes and 2.0% in other-PRDs, both  $p < 0.001$ ), though time required to achieve recovery was longer. The 5-year survival probability from day 91 of RRT among patients with scleroderma was 38.9% (95%CI: 32.0; 45.8%) while their 5-year post-transplantation patient survival and 5-year allograft survival were 88.2% (95% CI: 75.3; 94.6%) and 72.4% (95%CI: 55.0; 84.0%), respectively. The adjusted mortality from day 91 on RRT was higher among patients with scleroderma than observed in both control groups (hazard ratio: 1.25, 95%CI: 1.05; 1.48, and 2.00, 95%CI: 1.69; 2.39). In contrast, patient and graft survival after kidney transplantation did not differ between patients with scleroderma and control groups.

**Limitations:** No data on extra-renal manifestations, treatment, or recurrence.

**Conclusions:** Survival of patients with scleroderma who receive dialysis for more than 90 days was worse than for those with other causes of ESRD. Patient survival after transplantation was similar to that observed among patients with ESRD due to other conditions. Patients with scleroderma had higher rate of renal function recovery sufficient to stop RRT than controls.

## **Introduction**

**S**ystemic sclerosis (also referred to as scleroderma) is a rare chronic connective tissue disease with multi-organ involvement characterized by immune activation, vasculopathy, fibroblast dysfunction and excessive collagen accumulation in the skin and internal organs (253-255).

Renal disease in patients with scleroderma, particularly scleroderma renal crisis, result in significant morbidity and mortality (253). Scleroderma renal crisis typically manifests with an acute onset of accelerated hypertension, rapidly progressive renal failure, frequently accompanied by microangiopathic haemolytic anaemia and thrombocytopenia. Occurring in approximately 3-10% of the scleroderma population, severe renal disease is commonly seen in patients with diffuse rather than limited cutaneous scleroderma (253, 256). Until the 1970s, scleroderma renal crisis was recognized as the main cause of death in patients with scleroderma, though since the introduction of treatment with ACE inhibitors and reduction of corticosteroid doses the prognosis has substantially improved (256). Nevertheless, about 25-50% of patients with scleroderma renal crisis will develop ESRD and the mortality associated with this condition remains high (253, 255-259).

There is limited knowledge regarding the prevalence of scleroderma renal crisis requiring RRT (260) and due to the infrequency of this condition there are a limited number of large multicentre or registry-based studies available (255-259, 261-263). While the outcome of patients with scleroderma on dialysis seems to be uniformly worse than that of patients with other causes of ESRD (259, 263), the outcomes of kidney transplantation are less clear. It is known that renal function may recover after commencing RRT and there is an ongoing discussion regarding the optimal timing of kidney transplantation in patients with scleroderma (14, 257, 264).

We analysed the trends in incidence and prevalence of RRT for ESRD due to scleroderma in the ERA-EDTA Registry and determined the patient characteristics, patient survival on RRT, patient and graft survival after kidney transplantation and causes of death in a large cohort of European patients initiating RRT between 2002 and 2013.

## **Methods**

### **Patients and data collection**

The ERA-EDTA Registry collects data annually on patients starting RRT from national and regional renal registries in Europe. Renal registries sending individual patient level data to the ERA-EDTA Registry between 2002 and 2013, with at least 50% percent coverage

of the general population were included in the study. The renal registries included were Austria, Dutch-speaking Belgium, French-speaking Belgium, Denmark, Finland, Greece, Iceland, the Netherlands, Norway, the Spanish regional renal registries of Andalusia, Aragon, Asturias, Basque Country, Cantabria, Castile and León, Catalonia and Valencia, Sweden, United Kingdom: England, Northern Ireland and Wales, and United Kingdom: Scotland. The details of methods of data collection and data processing are described elsewhere (265). The cause of death was defined and categorized according to the ERA-EDTA coding system (265). All national and regional registries contributing data to the ERA-EDTA Registry followed national legislation with regard to ethics committee approval. Additional informed patient consent was not required for this study due to the de-identified nature of the information obtained.

### **Cases and matched control groups**

The incidence, prevalence and patient survival on RRT analyses refer to patients starting RRT for ESRD due to “systemic sclerosis (scleroderma)” [ERA-EDTA primary renal disease [PRD] code 87 (265)], as recorded by the responsible physician. Patient and graft survival after kidney transplantation refer to all patients with a diagnosis of scleroderma, or the matched controls (described below) who received their first kidney-only transplant between 1<sup>st</sup> January 2002 and 31<sup>st</sup> December 2013. This included patients who commenced RRT for ESRD before 2002. Age and sex were compared between scleroderma and non-scleroderma patients. We then formed two matched control groups of patients without scleroderma: 1) diabetes mellitus as a primary renal disease (PRD codes 80 and 81); and 2) patients without scleroderma and without diabetes mellitus as a primary renal disease, referred to as ‘other PRDs’. Due to the low number of scleroderma patients, we matched 10 controls to 1 case. We matched on age group at the start of RRT (5-year age groups) and sex, when comparing patients receiving RRT. When comparing transplant recipients we matched on age group at the time of kidney transplantation (5-year age groups) and sex.

### **Statistical analysis**

Time trends in the incidence of RRT per million population (pmp) were studied by year according to the date of RRT onset for all participating European countries/regions combined. Incidence was then assessed by country/region for the whole study period. Time trends in the prevalence of RRT pmp by year, defined as the number of patients alive and receiving RRT on 31<sup>st</sup> December of that year, divided by the mid-year general population, were studied for all participating European countries/regions. Incidence and prevalence rates were adjusted for age and sex using the European Standard Population

of 2005 as a reference (57). The time trends for the incidence rates and prevalence were estimated using Poisson regression, with the observed rate as the outcome and the year as the explanatory variable. The mean percentage annual change (MPAC) and its 95% confidence interval were computed from each model as  $[\exp(\beta)-1] \times 100$ , where  $\beta$  denotes the regression coefficient of time (i.e. change in the event rate per year). To examine whether the trends were linear, we performed Joinpoint regression analysis. 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 (58). This was performed using the Joinpoint software (version 4.0.4) (59).

To compare the characteristics of scleroderma patients receiving RRT with each of the matched control groups separately, the Wilcoxon signed-rank test was used for continuous variables with a skewed distribution and the McNemar square test for categorical variables. A two-tailed p-value <0.05 was considered as statistically significant. The first treatment modality was defined as treatment at day 91 after the start of RRT, as some patients received haemodialysis for a short period, while preparations were made for peritoneal dialysis.

The Kaplan-Meier method and Cox regression analysis were used for the survival analyses. The patient survival on RRT was examined for individuals who initiated RRT for ESRD due to scleroderma between 2002 and 2013, and was compared with each of the matched control groups separately. Day 91 after the onset of RRT was taken as the starting point for these survival analyses. The death of the patient was the event studied. Follow-up time was censored at recovery from RRT dependence, loss to follow-up and the end of the follow-up period (31<sup>st</sup> December 2013). Within the Cox regression analysis we took the strata (matched groups) into account. Patient survival on RRT was adjusted for time period (with three intervals, 2002-2005, 2006-2009 and 2010-2013) and country. Patient and graft survival after kidney transplantation was examined for patients who received their first transplant between 2002 and 2013 (regardless of the RRT start date). The scleroderma group was compared with each of the matched control groups separately. In these analyses the date of the first kidney transplant was defined as the first day of follow-up. For patient survival after transplantation, the event studied was death and in case of graft survival, the events were graft failure and death. Reasons for censoring were loss to follow-up and the end of follow-up period (31<sup>st</sup> December 2013). In the Cox regression analysis, patient and graft survival were adjusted for time period (as described above), country and donor type.

All analyses were performed using SAS 9.3 or Joinpoint software (59).

## Results

### Incidence and prevalence

A total of 342 patients with scleroderma were identified comprising 0.14% of 236,082 patients starting RRT between 2002 and 2013. The adjusted incidence of RRT for ESRD due to scleroderma between 2002 and 2013 was 0.18 pmp, ranging from 0.0 to 0.25 pmp between regions/countries (Table 12.1). The adjusted incidence of RRT for ESRD due to scleroderma was 0.26 pmp in 2002 and 0.12 pmp in 2013 (Table 12.2). There was a trend towards a decline in the incidence pmp over time but this did not reach statistical significance (MPAC: -3.6, 95%CI: -7.9; 0.8). During the study period, the adjusted prevalence of RRT for ESRD due to scleroderma varied between 0.73 and 0.95 pmp per year (Table 12.2) with a statistically significant increase in the prevalence pmp (MPAC: 2.0, 95%CI: 1.0; 2.9).

### Patient characteristics

Patients commencing RRT for ESRD due to scleroderma were significantly younger than patients (before matching) with other diagnoses (median age 59.9 years, [IQR: 50.2; 68.2] for patients with scleroderma versus 67.2 years, [IQR: 54.4; 76.1] for all non-scleroderma patients;  $p < 0.001$ ). The proportion of women within the scleroderma group was higher than that of non-scleroderma group (68.1% vs. 38.2%;  $p < 0.001$ ).

The group characteristics for the first 90 days or beyond the first 90 days are displayed in Table 12.3 for patients initiating RRT for ESRD due to scleroderma and for the control groups, matched on age group and sex. The treatment modality at day 91 after the start of RRT was different in patients with scleroderma compared with the matched control groups, with a higher percentage of haemodialysis in the scleroderma patients (Table 12.3,  $p \leq 0.01$  for both comparisons). A higher number of deaths during the first 90 days on RRT was observed in the scleroderma patients compared with both matched control groups (12.6% vs. 3.9% and 4.0% respectively, Table 12.3,  $p < 0.001$  for both comparisons).

The percentage of patients who recovered from RRT dependence during the first 90 days on RRT did not differ between the scleroderma patients and the matched control groups. However, a higher proportion of patients with scleroderma recovered from RRT dependence beyond this time period (7.6% vs. 0.7% and 2.0% in the matched control groups diabetes and other-PRDs, respectively; both  $p < 0.001$ ). In patients who recovered from RRT dependence, the time to recovery was longer in those with a diagnosis of

scleroderma than in both matched control groups (median of 255.5 days, [IQR: 130: 454] vs. 112.0 days, [IQR: 40.5; 178] for those with a PRD of diabetes and 167.5 days, [IQR: 60; 353] for those with other-PRDs, both  $p < 0.05$ ). The vast majority of patients who recovered from RRT dependence were female; 80.8% in patients with scleroderma, 83.2% for the matched control group with diabetes mellitus ( $p < 0.05$ ) and 60.0% in the other-PRDs matched control group ( $p < 0.001$ ). Median age was significantly lower in patients with scleroderma who recovered from RRT dependence than in both matched control groups (median 52.1 years, [IQR: 47.9; 56.8] vs. 64.6 years, [IQR: 54.8; 71.7] for those with a PRD of diabetes and 60.6 years, [IQR: 50.4; 66.3] for those with other-PRDs,  $p < 0.05$ ).

A total of 46 of the 342 (13.7%) scleroderma patients who started RRT between 2002 and 2013 received a kidney transplant during the study period. This percentage was 18.7% for the control group diabetes mellitus and 27.1% for the control group other-PRDs (both  $p < 0.001$  in comparison with patients with scleroderma).

Table 12.1. Incidence of renal replacement therapy (RRT) for ESRD secondary to scleroderma, by country/region from 2002 to 2013.

Country / Region	All RRT	Scleroderma			
	N	N	%	N pmp	N pmp*^
Austria	14650	12	0.08	0.12	0.12
Belgium: Dutch-speaking	13968	16	0.11	0.22	0.20
Belgium: French-speaking	9943	11	0.11	0.20	0.23
Denmark	8431	17	0.20	0.26	0.25
Finland	5775	8	0.14	0.13	0.11
Greece	26181	31	0.12	0.23	0.21
Iceland	295	0	0	0	0
Norway	5923	5	0.08	0.09	0.08
Spain: Andalusia	11817	11	0.09	0.11	0.12
Spain: Aragon	2031	3	0.15	0.19	0.18
Spain: Asturias	1772	2	0.11	0.15	0.14
Spain: Basque Country	3052	5	0.16	0.20	0.17
Spain: Cantabria	833	0	0	0	0
Spain: Castile and León	3654	8	0.22	0.27	0.23
Spain: Catalonia	12298	20	0.16	0.23	0.24
Spain: Valencia	8582	7	0.08	0.12	0.12
Sweden	13640	19	0.14	0.17	0.17
the Netherlands	22131	37	0.17	0.19	0.19
United Kingdom	71106	130	0.18	0.19	0.19
All countries	236082	342	0.14	0.18	0.18

\*Pmp=per million population. ^N pmp are adjusted for the age and sex distribution using the European Standard Population of 2005 as reference.

Table 12.2. Incidence and prevalence of renal replacement therapy for end-stage renal disease secondary to scleroderma per million population by year from 2002 to 2013 and the mean percentage annual change (MPAC) with 95% confidence interval (95%CI) for all countries/regions combined, adjusted for age and sex using the European Standard Population of 2005 as a reference.

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	MPAC (95%CI)
Incidence	0.26	0.22	0.20	0.20	0.17	0.20	0.20	0.11	0.15	0.27	0.14	0.12	-3.6 (-7.9; 0.8)
Prevalence	0.80	0.75	0.73	0.81	0.81	0.90	0.89	0.88	0.85	0.95	0.95	0.89	2.0 (1.0; 2.9)

Table 12.3. Characteristics of patients starting RRT for ESRD according to primary cause of kidney disease (scleroderma, diabetes mellitus or other PRDs) and time since RRT.

	Scleroderma	Control group*: DM	Control group*: Other PRDs
<b>First 90 days of commencing RRT</b>			
Patients at day 1 of RRT, N	342	3420	3420
Female at day 1 of RRT, %	68.1	68.1	68.1
Age at day 1 of RRT, yrs, median, (IQR)	59.9 (50.2; 68.2)	59.8 (50.3; 68.1)	59.8 (50.3; 68.2)
Patients who recovered from RRT dependence within 90 days, N (%)	3 (0.9)	21 (0.6)	38 (1.1)
Patients who died within 90 days, N (%)	43 (12.6)	135 (3.9)	138 (4.0)
Loss to follow-up/missing data within 90 days, N (%)	0 (0)	7 (0.2)	15 (0.4)
Treatment discontinued/limited care within 90 days, N (%)	0 (0)	4 (0.1)	5 (0.2)
<b>Beyond 90 days of commencing RRT</b>			
Patients at day 91 after start of RRT, N (as a % of patients at day 1)	296 (86.5)	3253 (95.1)	3224 (94.3)
Female at day 91 of RRT, %	67.2	67.9	68.4
Age at day 91 of RRT, yrs, median (IQR)	58.6 (49.4; 68.1)	59.9 (50.2; 68.2)	59.6 (49.9; 68.1)
Treatment modality at day 91, %			
Haemodialysis	83.4	75.9	70.4
Peritoneal dialysis	14.9	20.6	22.5
Transplantation	1.7	3.5	7.1
Time to recovery from RRT dependence, days, median (IQR)	255.5 (130.0; 454.0)	112.0 (40.5; 178.0)	167.5 (60.0; 353.0)

\*The matched-control groups were matched on day 1 of renal replacement therapy (RRT), based on age group and sex. # DM: diabetes mellitus as primary renal disease; the matched control groups did not include patients with scleroderma.

### **Patient survival on RRT**

Figure 12.1a depicts the 5-year patient survival on RRT after day 91 for patients who started RRT for ESRD due to scleroderma (38.9%, 95%CI: 32.0; 45.8) and for the matched control groups diabetes mellitus (46.0%, 95%CI: 43.9; 48.0) and other-PRDs (63.6%, 95%CI: 61.6; 65.6). After adjustment for time period and country, the mortality from day 91 after the commencement of RRT was higher in patients with scleroderma than in both matched control groups (i.e. diabetes and other-PRDs, HR: 1.25, 95%CI: 1.05; 1.48, and 2.00, 95%CI: 1.69; 2.39, respectively; Figure 12.2a).

### **Patient and graft survival after kidney transplantation**

Of the 57 patients with scleroderma who received their first kidney transplant between 2002 and 2013, the percentage of patients with a living donor transplant was 35.6% in the scleroderma group and 17.8% and 29.8% in the matched control groups of diabetes and other-PRDs respectively. The median time on dialysis before receiving their first transplant was significantly greater in the patients with scleroderma (2.9, IQR: 1.6; 4.7 years) compared with the matched control groups (diabetes: 1.6 years, IQR: 0.8; 2.9 and other-PRDs: 1.6 years, IQR: 0.5; 3.6, both  $p < 0.001$ ). Figure 12.1b and 12.1c present the 5-year patient and graft survival after receiving a first kidney transplant, respectively, for patients with scleroderma (88.2%, 95%CI: 75.3; 94.6 and 72.4%, 95%CI: 55.0; 84.0) and for the matched control groups with diabetes mellitus (84.3%, 95%CI: 80.5; 87.4 and 76.5%, 95%CI: 72.2; 80.3) and other-PRDs patients (89.3%, 95%CI: 86.0; 91.8 and 81.5%, 95%CI: 77.6; 84.8), matched on age group at kidney transplantation and sex. The risk of death for patients with scleroderma after kidney transplantation, adjusted for country, time period and donor type, did not differ from patients with diabetes or other-PRDs (Figure 12.2b). Similarly, graft survival adjusted for country, time period and donor type did not differ between the patients with scleroderma and the matched control groups (Figure 12.2c).

### **Causes of death**

Table 12.4 shows the causes of death for patients who started RRT for ESRD due to scleroderma and for the matched control groups since day 91. Patients with scleroderma had fewer deaths due to cardiovascular events (particularly myocardial ischaemia and cardiac arrest) compared with the matched control group of patients with diabetes. Compared with the matched control group of patients with non-other-PRDs, there were fewer deaths due to malignancy and cardiac arrest among the patients with scleroderma. Conversely, there were more deaths due to heart failure. A large proportion of deaths in the patients with scleroderma were reported as “miscellaneous” or unknown.

Figure 12.1. Kaplan-Meier survival analyses of (a) patient survival on RRT for ESRD secondary to scleroderma (N=296) from day 91 and for the matched control groups\* with either DM (N=3253) as a PRD or other-PRDs (N=3224). Control groups are matched on 5-year age groups at the onset of RRT and sex. Median age was 59.9 years and 68.1% were female in the scleroderma group and in each matched control group; (b) patient survival after kidney transplantation for ESRD secondary to scleroderma (N=57) and for the matched control groups\*^ (N=565 for each matched control group); (c) graft survival after kidney transplantation for ESRD secondary to scleroderma (N=57) and for the matched control groups\* (N=565 for each matched control group). ^Control groups are matched on 5-year age groups at the time of transplantation and sex. Median age was 49 years and 62.7% were female in the scleroderma group and in each matched control group. \*The matched control groups did not include patients with scleroderma.

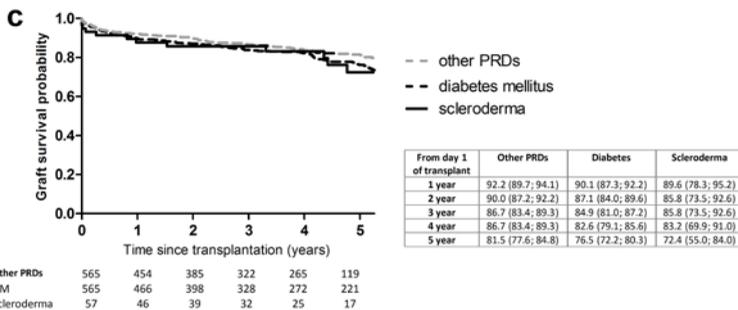
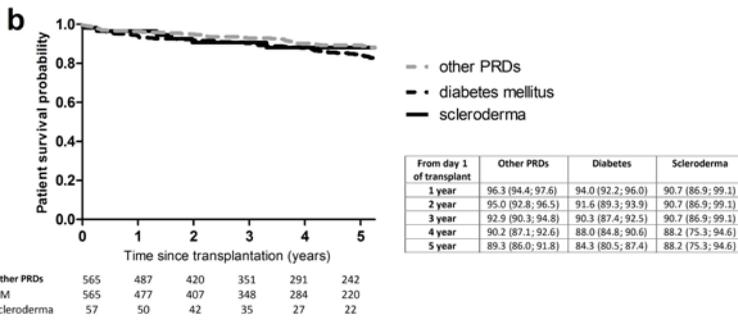
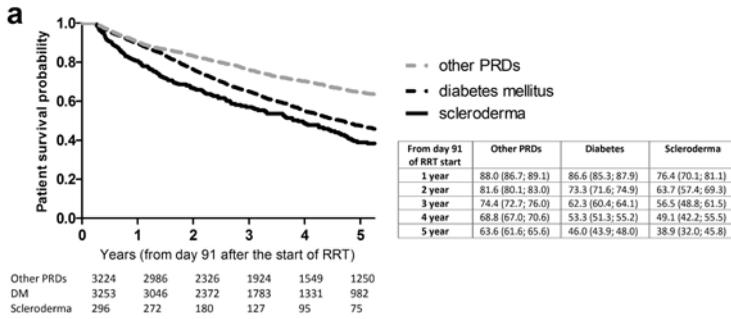
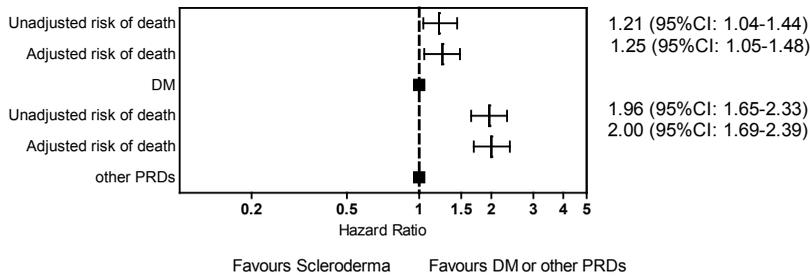
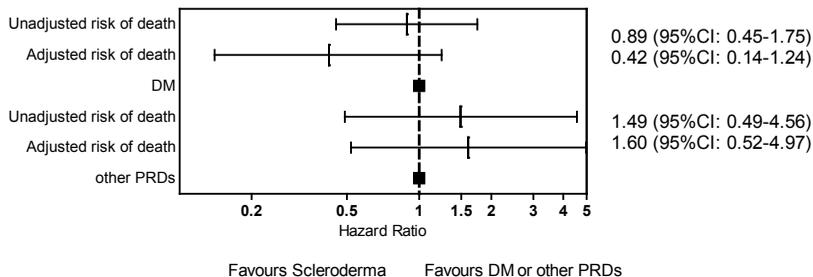


Figure 12.2. Hazard ratios (HR; 95% confidence intervals) for (a) death on RRT from day 91 for patients with scleroderma versus the matched control groups\*, unadjusted and adjusted for time period and country. Control groups with either DM as a PRD or other-PRDs are matched on 5-year age groups at the onset of RRT and sex. The scleroderma group and each matched control group had a median age of 59.9 years and 68.1% were female; (b) death after kidney transplantation for patients with scleroderma versus the matched control groups\*^, unadjusted and adjusted for time period, country and donor type; (c) graft failure after kidney transplantation in patients with scleroderma versus the matched control groups\*^, unadjusted and adjusted for time period, country and donor type. ^Control groups with either DM as a PRD or other-PRDs are matched on 5-year age groups at the time of transplantation and sex. The scleroderma group and each matched control group had a median age of 49 years and 62.7% were female. \*The matched control groups did not include patients with scleroderma.

a. Risk of death after day 91 of commencing RRT: patients with scleroderma versus matched DM or 'other PRDs' groups.



b. Risk of death after kidney transplantation: patients with scleroderma versus matched DM or 'other PRDs' groups.



c. Risk of graft failure after kidney transplantation: patients with scleroderma versus matched DM or 'other PRDs' groups.

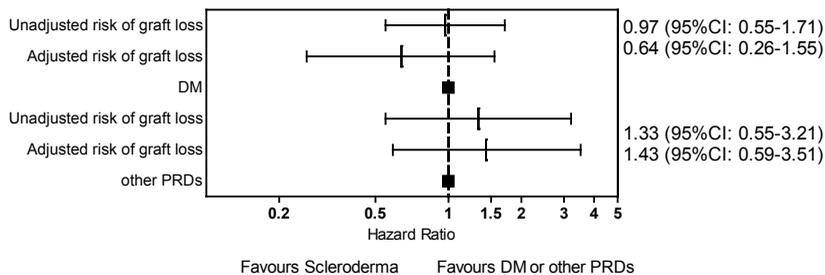


Table 12.4. Causes of death in patients starting RRT for ESRD secondary to scleroderma and the matched control groups since day 91.

	Scleroderma N=296	Control group*: DM N=3,253	Control group*: other-PRDs N= 3,224
Number of deaths (%)	156 (52.7)	1,613 (49.6)	1,134 (35.2)
Cause of death	%	%	p-value#
Cardiovascular disease	21.2	36.3	<0.001
Myocardial ischaemia / infarction	4.5	12.8	0.002
Heart failure	8.3	5.3	0.1
Cardiac arrest; other cause /unknown	3.9	12.0	0.002
Cerebrovascular accident	4.5	6.2	0.4
Infection	14.1	17.3	0.3
Suicide/refusal of dialysis	3.9	1.7	0.06
Withdrawal from dialysis	5.8	5.8	0.9
Cachexia	3.9	1.6	0.04
Malignancy	1.9	3.8	0.2
Miscellaneous	19.2	12.7	0.02
Unknown/unavailable/missing	30.1	20.8	0.007

Percentages may not add up to 100% because of rounding off. DM: diabetes mellitus as primary renal disease.

\*Control groups are matched on 5-year age groups and sex; # comparison of control group with patients with scleroderma. The matched control groups did not include patients with scleroderma.

## Discussion

Systemic sclerosis is a very rare cause of ESRD and as such analysis of this condition requires multi-centre, multi-national studies performed over a long period of time. This study describes the characteristics and outcomes of patients with scleroderma requiring RRT in a large European cohort. We found that the age and sex adjusted incidence of RRT for ESRD due to scleroderma between 2002 and 2013 was only 0.18 pmp. There was a trend towards a decline in the incidence over time but this did not reach statistical significance. Conversely the prevalence significantly increased over the time period from 0.80 pmp in 2002 to 0.89 pmp in 2013. Furthermore, we observed that survival on RRT in patients with scleroderma was worse than in other causes of ESRD, whilst transplant recipients with scleroderma showed a similar survival to the control groups.

Scleroderma is a rare disease with an estimated annual incidence of 10-20 pmp and a prevalence of about 30-300 pmp. The occurrence of scleroderma is presumed to be higher in North America or Australia than in Europe or Asia, even though epidemiological studies are difficult to perform due to the low incidence and heterogeneity of the disease (266, 267). The overall prevalence of scleroderma in the general population has been

reported to increase, probably due to a greater awareness of the disease and improved patient survival (268), whereas there is in more recent studies some evidence suggesting a lower incidence of scleroderma renal crisis (253). In keeping with this observation, we observed a non-statistically significant trend towards a decline in the incidence of RRT for ESRD due to scleroderma over time. However, as frequently seen in rare diseases with low numbers of patients, the number of cases in each year fluctuated. In Australia and New Zealand the incidence of patients with scleroderma requiring RRT for ESRD declined significantly between 2002 and 2013, from 0.51 pmp to 0.18 pmp (269). The prevalence of RRT for ESRD caused by scleroderma increased during the study period. This is most likely explained by the improved survival of patients with scleroderma receiving RRT.

In this study, patients with scleroderma were less likely to be treated with peritoneal dialysis than haemodialysis when compared with the matched control groups. This is in contrast to the data from the Australian and New Zealand registry where the use of peritoneal dialysis was more common in patients with scleroderma than in patients with other causes of ESRD. However, peritoneal dialysis is also a more frequent treatment option for ESRD in Australia than in Europe (263). The choice of the “optimal” modality of RRT in patients with scleroderma is generally considered problematic (270).

Scleroderma has long been recognized as a condition with a relatively high probability of renal recovery, even in patients requiring long-term dialysis (271). This has important implications regarding the timing of kidney transplantation and some authors have recommended treating patients initially with dialysis for up to two years (264), whereas, for instance, the Canadian guidelines suggest that kidney transplantation could be considered in patients with scleroderma who have had quiescent disease for at least six months off cytotoxic agents and have limited extra-renal disease (14). Previous reports have described renal recovery in patients with scleroderma to be as high as 38% (253, 258). However the Australian and New Zealand Registry, which includes patients with presumed ESRD (263), reported renal recovery at 10%, which is similar to the 7.6% observed in our study. The proportion of patients with presumed ESRD who recovered renal function in this study was higher in patients with ESRD secondary to scleroderma than in patients with other causes of ESRD. It has been previously noted that systemic autoimmune diseases commonly show higher recovery rates than other PRDs (272, 273). Importantly, 25% of patients who recovered renal function in the current study discontinued dialysis after more than 15 months of RRT, supporting the recommendation of delaying kidney transplantation in these patients. This may explain why the time spent on dialysis before transplantation was longer in patients with scleroderma than in the matched control

groups in our study.

In previous studies exploring the survival of patients with scleroderma receiving RRT, a diagnosis of scleroderma mostly showed unfavourable outcomes (259, 263, 273) and was even identified as an independent predictor of death (HR: 2.47, 95%CI: 1.99; 3.05) (263). Similarly, in the present study, we confirmed that both early and long-term mortality of patients with scleroderma receiving RRT remains high and that the prognosis is worse than that of RRT patients with diabetes. Among the causes of death, cardiovascular events, especially ischemic heart disease, were much less common in patients with scleroderma than in patients with diabetes. Nevertheless, detailed evaluation of the causes of death was limited due to the high number of unknown or miscellaneous causes reported in the patients with scleroderma.

Interestingly, patient and graft survival after kidney transplantation did not differ between patients with scleroderma and other PRDs. Given the poorer survival outcomes in patients with scleroderma, but similar post-transplant survival outcomes one must consider it likely that bias towards transplanting patients with scleroderma without major comorbidities i.e. the healthiest patients exists. Furthermore given the small sample size one cannot rule out a possible type 2 error. Nevertheless, our findings support the use of kidney transplantation in at least some patients with scleroderma, preferably those without major extra-renal complications, although transplantation should be delayed due to the aforementioned chance of renal recovery. The 5-year graft survival rate of 72.4% in our study is greater than the 3-year graft survival of 60.3% in the study by Gibney et al. (262), or the 5-year graft survival of 56.7% in the study by Pham et al. (274), both using US data. Although direct comparison is hardly possible, it may suggest improving survival over time, even though there are known geographical differences, with a somewhat better graft survival in Europe than in the US (275).

We are aware of the potential limitations of this study that include the registry-based nature of the data with a lack of detailed information regarding the disease course of individual patients, for example, disease duration prior to RRT, renal biopsy results, extent of extra-renal involvement, administered treatment, or disease recurrence after kidney transplantation. It should be noted that the patients included in this study originated from eleven countries over a 12-year period. It is possible that country differences in the selection criteria for transplantation and a temporal effect may in part account for some of the differences we observed between the groups. As such there are known and unknown factors which we cannot take into account within this study.

It is known that ESRD in some patients with scleroderma is not necessarily caused solely by scleroderma renal crisis, they may have for example normotensive renal crisis, penicillamine-associated nephropathy, scleroderma-associated vasculopathy, a mixed disease and overlap with for example, ANCA-associated vasculitis, in which case their renal survival and renal outcomes may be different (253, 276). However, we were not able to distinguish such mixed causes of ESRD. Furthermore, on occasion it may be difficult to differentiate between acute cases of kidney failure requiring short-term (but prolonged) dialysis from true ESRD in patients with a diagnosis of scleroderma. The view regarding such patients may differ between registries, some of which may not enter patients who recovered renal function as ESRD into the database, even though the time on dialysis exceeded three months which is typically the cut-off point for entering a patient requiring long-term RRT into the ESRD registry. In addition we do not have access to comorbidity data including diabetic status (beyond diabetes mellitus as a cause of ESRD). Having data on patient co-morbidities is required to further differentiate patients, for example, this information could have in part, accounted for the differences in transplantation rates and time to transplantation between patients with a diagnosis of scleroderma and the control groups. Nor do we have data on vascular access. Problems related to vascular access in patients with scleroderma may have contributed to differences in RRT outcomes when compared to control patients, which we are not aware of. On the other hand, the ERA-EDTA Registry provides a unique opportunity to analyse a large cohort of European patients with scleroderma receiving RRT and also allows for the direct comparison of patients with scleroderma with other causes of ESRD.

In conclusion, we show that the overall survival of patients with scleroderma receiving RRT is worse than that of patients with ESRD due to diabetes or other PRDs. Although limited by a relatively low number of patients, our results suggest that kidney transplantation may be a sound therapeutic option in some patients with ESRD due to scleroderma, as graft and patient survival rates in this study were comparable with other non-diabetic causes of ESRD.