KI REPORTS
KIReports.org
CLINICAL RESEARCH

End-Stage Kidney Disease From Scleroderma in the United States, 1996 to 2012

Donal J. Sexton[1,2], Scott Reule[1] and Robert N. Foley[1]

[1]Division of Renal Diseases and Hypertension, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA; and [2]Health Research Board Clinical Research Facility, National University of Ireland Galway, Galway, Ireland

Introduction: Although the management of scleroderma continues to evolve, it is unknown whether the burden of end-stage kidney disease (ESKD) treated with maintenance renal replacement therapy from SD has changed.

Methods: We examined United States Renal Data System data (n = 1,677,303) for the years 1996 to 2012 to quantify the incidence and outcomes of ESKD from scleroderma treated with renal replacement therapy (n = 2398). Outcomes assessed through demography-matched scleroderma-positive/scleroderma-negative comparisons included recovery of kidney function, mortality, listing for transplant, renal transplantations, and graft failure.

Results: Overall ESKD rates from scleroderma were 0.5 per million per year. Adjusted incidence ratios fell over time, to 0.42 in 2012 (vs. 1996, 95% confidence interval [CI] = 0.32−0.54, $P < 0.001$). Adjusted incidence ratios for ESKD from scleroderma fell over time in both sexes, all age, race, and ethnicity categories except age < 20 years and Asian race, and in all regions of the United States. After initiating renal replacement therapy, patients with scleroderma had a greater likelihood of recovery of kidney function (hazards ratio [HR] = 2.67, 95% CI = 1.90−3.76, $P < 0.001$) and death (HR = 1.44, 95% CI = 1.34−1.54, $P < 0.001$) and a lower likelihood of transplantation (HR = 0.51, 95% CI = 0.44−0.59, $P < 0.001$) than demography-matched patients without scleroderma.

Conclusion: The incidence of ESKD from scleroderma appears to have declined in the United States since 1996. ESKD from scleroderma is associated with an enhanced likelihood of recovery of kidney function and death, a reduced likelihood of transplantation, and similar outcomes after transplantation.

Kidney Int Rep (2018) **3,** 148–154; https://doi.org/10.1016/j.ekir.2017.09.003
KEYWORDS: dialysis; end-stage kidney disease; recovery; scleroderma; transplant

Scleroderma, a rare disorder associated with considerable morbidity and mortality, has an estimated annual incidence of 10 to 12 per million in the United States.[1,2] End stage kidney disease (ESKD) is a feared complication that may occur abruptly as a scleroderma renal crisis, or as more indolent, progressive deterioration of kidney function.[3−11]

The therapeutic approach to scleroderma has evolved substantially in recent years, particularly with regard to angiotensin-converting enzyme inhibitor use in scleroderma renal crisis and vasodilator therapy for pulmonary hypertension.[12−14] As management of scleroderma has continued to evolve, it seems natural to question whether reductions in ESKD have occurred, and, if so, whether salutary trends have been generalized across major demographic subgroups. Hence, we set out to describe the clinical epidemiology of ESKD from scleroderma in the United States between 1996 and 2012.

MATERIALS AND METHODS

Study Objectives

The principal objective of this study was to evaluate trends in demography-adjusted incidence ratios of ESKD from scleroderma necessitating RRT in the United States between 1996 and 2012. For secondary outcomes after initiation of renal replacement therapy (RRT), we set out to compare likelihoods of renal recovery (where RRT was no longer necessary), listing for renal transplant, transplantation, death, and graft failure in matched patients with and without scleroderma. We further aimed to calculate hazards ratios for these outcomes, specific to the scleroderma population.

Study Subjects

In this retrospective study, we used data from the United States Renal Data System (USRDS) for patients

Correspondence: Donal Sexton, HRB Clinical Research Facility, National University of Ireland Galway, University Road, Galway, Ireland H91 TK33 E-mail: dosexton@tcd.ie

Received 7 February 2017; revised 7 September 2017; accepted 11 September 2017; published online 15 September 2017

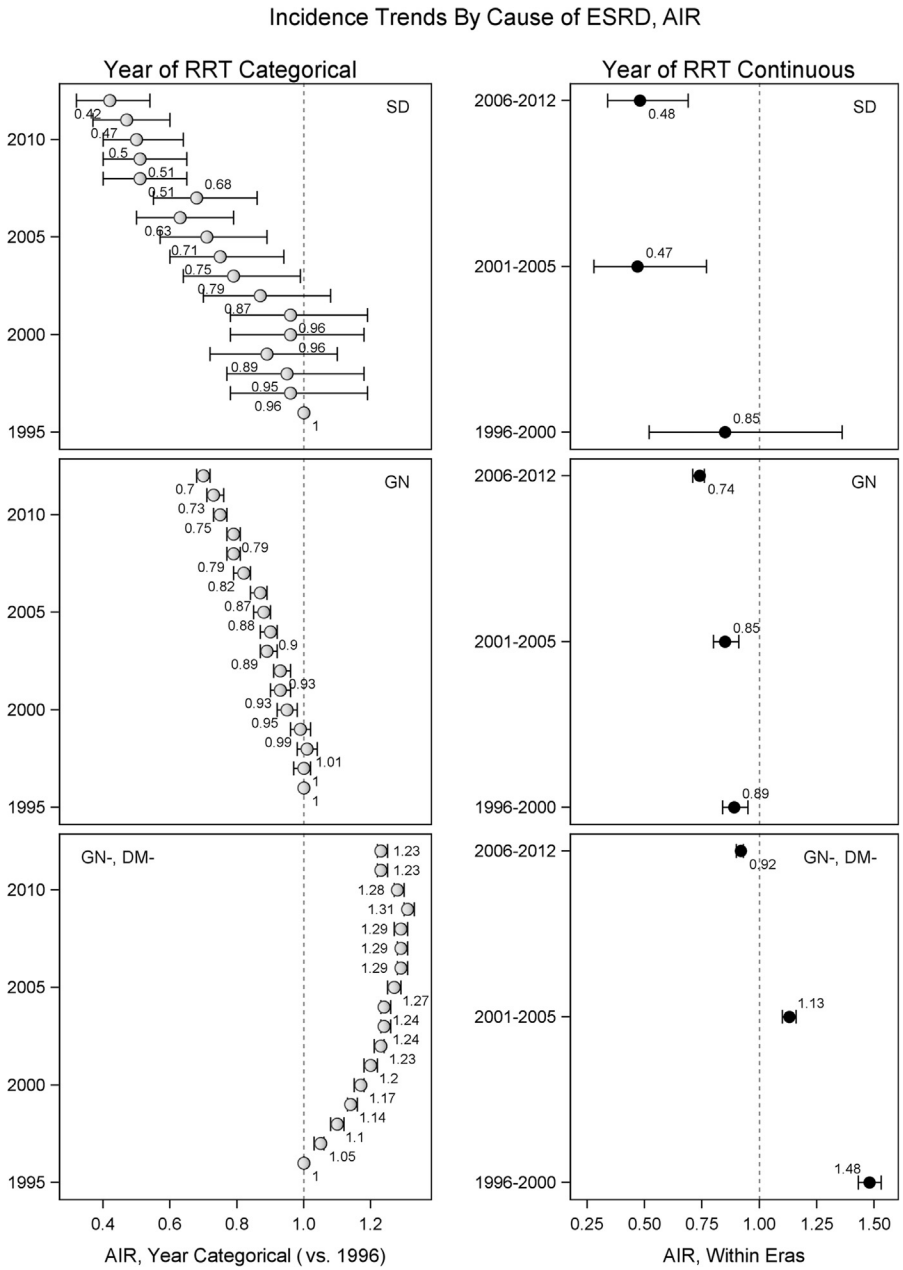

Figure 1. Trends in adjusted incidence ratios of end-stage kidney disease (ESKD) from scleroderma and other causes, 1996 to 2012. AIR, adjusted incidence ratio; DM, diabetes mellitus; GN, glomerulonephritis; RRT, renal replacement therapy.

who initiated maintenance RRT in the United States between 1996 and 2012 (N = 1,677,303). Baseline characteristics at initiation of RRT were determined from the Centers for Medicare & Medicaid (CMS) Medical Evidence Report (form CMS-2728). By federal requirement, this form must be submitted for all new patients starting RRT in the US. The Medical Evidence Form changed in 2005. On both forms, 1 of 82 causes is entered as the primary cause of ESKD, with identical options in the 1995 and 2005 forms. For this study, scleroderma cases were those with primary cause of ESKD listed as "Scleroderma" in the Medical Evidence Form. Dates of death, recovery of renal function, first listing for transplant, first renal transplantation, and graft failure were used to define clinical outcomes occurring after first RRT.

Analysis

Mid-year US census data were used for population denominators for the years examined, with age in 5-year increments. Poisson regression was used to calculate incidence ratios of RRT-requiring ESKD from scleroderma, as well as for graphical illustration of annual trends of ESKD from glomerulonephritis or from causes other than diabetes and glomerulonephritis. The χ^2 test was used for unadjusted comparisons of patients with and without scleroderma, and logistic regression for adjusted comparisons. For comparisons of clinical

Table 1. Adjusted incidence ratios of end-stage kidney disease due to scleroderma, requiring renal replacement therapy, 1996 to 2012 (N = 2400)

	Incidence ratios, overall population			
Era	Unadjusted incidence ratio	Adjusted incidence ratio		
Year as a continuous variable, per 10 yr	0.61 (0.56–0.66)	0.58 (0.54–0.63)	—	—
Categorical			—	—
1996	1 (Reference)	1 (Reference)	—	—
1997	0.96 (0.78–1.19)[a]	0.96 (0.78–1.19)[a]	—	—
1998	0.96 (0.78–1.19)[a]	0.95 (0.77–1.18)[a]	—	—
1999	0.90 (0.73–1.12)[a]	0.89 (0.72–1.1)[a]	—	—
2000	0.98 (0.79–1.21)[a]	0.96 (0.78–1.18)[a]	—	—
2001	0.98 (0.8–1.21)[a]	0.96 (0.78–1.19)[a]	—	—
2002	0.90 (0.72–1.11)[a]	0.87 (0.7–1.08)[a]	—	—
2003	0.82 (0.66–1.02)[a]	0.79 (0.64–0.99)[b]	—	—
2004	0.78 (0.62–0.97)[b]	0.75 (0.6–0.94)[b]	—	—
2005	0.74 (0.59–0.93)[c]	0.71 (0.57–0.89)[c]	—	—
2006	0.66 (0.52–0.83)	0.63 (0.5–0.79)	—	—
2007	0.72 (0.57–0.9)[c]	0.68 (0.55–0.86)	—	—
2008	0.54 (0.42–0.69)	0.51 (0.4–0.65)	—	—
2009	0.54 (0.42–0.69)	0.51 (0.4–0.65)	—	—
2010	0.54 (0.42–0.69)	0.5 (0.4–0.64)		
2011	0.51 (0.4–0.65)	0.47 (0.37–0.60)	Incidence ratios for calendar year as continuous variable within subgroups, per decade	
2012	0.45 (0.35–0.58)	0.42 (0.32–0.54)	Unadjusted	Adjusted
Age < 20 yr	0.01 (0.01–0.02)	0.01 (0.01–0.02)	0.56 (0.19–1.62)[a]	0.57 (0.20–1.65)[a]
Age 20–39 yr	0.20 (0.18–0.23)	0.20 (0.18–0.23)	0.56 (0.43–0.72)	0.55 (0.43–0.72)
Age 40–64 yr	1 (Reference)	1 (Reference)	0.55 (0.49–0.62)	0.56 (0.50–0.62)
Age 65–79 yr	1.68 (1.53–1.84)	1.61 (1.47–1.76)	0.64 (0.54–0.74)	0.65 (0.56–0.76)
Age ≥ 80 yr	0.50 (0.40–0.63)	0.44 (0.35–0.56)	0.54 (0.34–0.86)[c]	0.55 (0.34–0.88)[b]
Male sex	1 (Reference)	1 (Reference)	0.65 (0.55–0.76)	0.60 (0.51–0.72)
Female sex	3.06 (2.78–3.36)	2.83 (2.58–3.11)	0.60 (0.55–0.66)	0.58 (0.52–0.63)
White race	1 (Reference)	1 (Reference)	0.54 (0.45–0.66)	0.65 (0.53–0.79)
African American/black race	1.49 (1.35–1.65)	1.84 (1.65–2.04)	0.66 (0.60–0.72)	0.64 (0.58–0.71)
Native American race	0.73 (0.47–1.15)[a]	1.07 (0.68–1.68)[a]	0.35 (0.14–0.91)[b]	0.35 (0.13–0.92)[b]
Asian race	0.47 (0.36–0.63)	0.56 (0.43–0.75)	0.86 (0.49–1.51)[a]	0.77 (0.44–1.36)[a]
Non-Hispanic ethnicity	1 (Reference)	1 (Reference)	0.7 (0.64–0.76)	0.65 (0.59–0.70)
Hispanic ethnicity	0.47 (0.41–0.55)	0.83 (0.71–0.98)[b]	0.57 (0.42–0.78)	0.53 (0.39–0.72)
Northeastern region	1 (Reference)	1 (Reference)	0.72 (0.6–0.86)	0.69 (0.58–0.82)
Midwestern region	0.98 (0.87–1.11)[a]	1.02 (0.91–1.15)[a]	0.70 (0.59–0.82)	0.67 (0.56–0.78)
Southern region	0.83 (0.74–0.93)[c]	0.84 (0.75–0.94)[c]	0.5 (0.43–0.58)	0.47 (0.41–0.55)
Western region	0.72 (0.64–0.82)	0.89 (0.78–1.01)[a]	0.62 (0.51–0.75)	0.59 (0.49–0.71)

[a] $P \geq 0.05$.
[b] $0.01 \leq P < 0.05$.
[c] $0.001 \leq P < 0.01$.
Note: Of 2400 patients, 2385 (99.4%) with scleroderma had documentation of age, sex, ethnicity, and geographic region and had race categories corresponding to those used in the census summaries ("Native American," "Asian," "black," "white"). Incidence ratios are reported with 95% confidence intervals in parentheses. Adjustment factors were year, age, sex, race, ethnicity, and region.
$P < 0.001$ unless otherwise indicated.

outcomes, patients with and without scleroderma were matched by calendar year, age, sex, race, ethnicity, and region of the United States. Poisson regression and Cox regression, respectively, were used to calculate incidence ratios of scleroderma and scleroderma-positive/scleroderma-negative—adjusted hazards ratios (AHRs) for events occurring after initiation of RRT, with follow-up ending on 30 June 30 2013. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate glomerular filtration rate at RRT initiation.[15] The Fine and Gray proportional hazards method was used for calculating hazards ratios of clinical events,[16] with death, recovery of renal function, and renal transplant as competing events, using the "eventcode" option in the "phreg" function of SAS software version 9.1.4 (SAS Institute, Cary, NC), the program used for all data analysis.

RESULTS

The crude incidence rate of ESKD from scleroderma between 1996 and 2012 was 0.5 cases per million per year

Table 2. Comparisons of patients with and without scleroderma at initiation of renal replacement therapy, at listing for renal transplant, and at renal transplantation

	At initiation of renal replacement therapy			At listing for renal transplant			At renal transplantation		
	Scleroderma			Scleroderma			Scleroderma		
Characteristic	Yes 2398	No 1,680,073	AOR scleroderma (yes vs. no)	Yes 392	No 246,421	AOR scleroderma (yes vs. no)	Yes 260	No 203,594	AOR scleroderma (yes vs. no)
ESKD from diabetes	0	44.5	—	0	40.0	—	0	30.2	—
ESKD from hypertension	0	27.9	—	0	22.2	—	0	18.0	—
ESKD from other cause	100	27.6	—	100	37.8	—	100	51.8	—
Era 1996–2000	35.2	24.9	1 (Reference)	23.2	19.1	—	20	17.2[b]	—
Era 2001–2005	32.7	29.6	0.82 (0.74–0.90)	36.0	29.8	1.05 (0.81–1.37)[a]	38.5	32.0[b]	1.04 (0.74–1.45)[a]
Era 2006–2012	32.1	45.6	0.53 (0.48–0.59)	40.8	51.1	0.73 (0.56–0.94)[b]	41.5	50.9[b]	0.72 (0.51–1.01)[a]
Age < 40 yr	11.2	9.4	1 (Reference)	15.1	24.8	1 (Reference)	12.3	29.1	—
Age 40–64 yr	57.5	41.4	1.13 (0.99–1.29)[a]	74.0	62.3	2.01 (1.51–2.66)	76.2	58.3	3.23 (2.22–4.7)
Age 65–79 yr	28.1	35.9	0.52 (0.45–0.60)	11.0	12.7	1.38 (0.93–2.05)[a]	11.5	12.4	2.36 (1.43–3.91)
Age ≥ 80 yr	3.2	13.3	0.15 (0.12–0.20)	0	0.2	—	0	0.2	—
Female sex	75.9	44.8	4.13 (3.76–4.54)	78.8	38.9	6.19 (4.85–7.89)	78.1	39.3	5.75 (4.28–7.71)
White race	77.6	66.1	1 (Reference)	78.8	60.0	—	86.2	70.2	—
African American/black race	18.9	28.4	0.41 (0.37–0.46)	17.3	32.1	0.34 (0.26–0.45)	10.4	23.1	0.35 (0.23–0.52)
Other race	3.5	5.5	0.44 (0.35–0.54)	3.8	7.9	0.30 (0.18–0.51)	3.5	6.7	0.38 (0.19–0.75)[c]
Hispanic	7.3	11.8	0.43 (0.36–0.50)	10.2	16.9	0.44 (0.31–0.61)	9.2	13.0[a]	0.64 (0.42–0.99)[b]
Northeast	21.7	18.2	1 (Reference)	23.5	18.9	—	26.5	19.0[c]	—
Midwest	25.1	21.8	0.87 (0.78–0.98)[b]	25.5	19.7	0.94 (0.70–1.24)[a]	25.0	24.3[c]	0.68 (0.49–0.96)[b]
South	34.3	40.4	0.72 (0.64–0.80)	28.8	38.3	0.66 (0.50–0.86)[c]	28.5	36.0[c]	0.61 (0.44–0.85)[b]
West	18.9	19.7	0.84 (0.74–0.96)[c]	22.2	23.1	0.83 (0.61–1.12)[a]	20.0	20.7[c]	0.70 (0.49–1.01)[a]
On dialysis > 1 yr	—	—	—	57.1	48.7	1.60 (1.31–1.97)	77.3	62.0	2.69 (2.00–3.63)
Hemodialysis as first RRT	92.5	90.5	—	79.8	81.4[a]	—	91.0	92.0[a]	—
Peritoneal dialysis as first RRT	6.8	7.5	0.64 (0.54–0.75)	20.2	18.6	0.91 (0.71–1.18)[a]	9.0	8.0[a]	0.85 (0.52–1.39)[a]
Transplant as RRT as first RRT	0.8	2	0.21 (0.13–0.34)	—	—	—	—	—	—
Vascular disease	19.2	34.2	0.49 (0.44–0.54)	—	—	—	—	—	—
Diabetes	7.5	50.8	0.07 (0.06–0.08)	—	—	—	—	—	—
Malignancy	3.3	6.6	0.58 (0.46–0.73)	—	—	—	—	—	—
Smoking	5.8	5.7[a]	0.93 (0.78–1.10)[a]	—	—	—	—	—	—
Alcohol/drug abuse	2	2.4[a]	0.99 (0.74–1.32)[a]	—	—	—	—	—	—
eGFR > 15 ml/min per 1.73 m^2	9.2	11.2[c]	0.93 (0.81–1.07)[a]	—	—	—	—	—	—
Body mass index ≥ 30	8.5	32.2	0.15 (0.13–0.17)	—	—	—	—	—	—
Serum albumin < 3.5 g/dl	71.9	64.5	1.42 (1.29–1.58)	—	—	—	—	—	—
Hemoglobin ≥ 9 g/dl	70.7	71.3[a]	1.02 (0.93–1.12)[a]	—	—	—	—	—	—
Living donor	—	—	—	—	—	—	49.2	38.3	1.45 (1.13–1.85)

AOR, adjusted odds ratio; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease. Parameter estimates are presented as column percentages or odds ratios, with 95% confidence intervals in parentheses. Estimates for age, duration of dialysis therapy, and mode of dialysis therapy refer to the day of initiation of RRT, listing for transplant, and renal transplantation, respectively. Comorbid conditions were assessed only at initiation of RRT. Statistical comparisons are of patients with and without scleroderma at initiation of RRT, listing for transplant, and renal transplantation. Logistic regression–adjusted for age, sex, race, ethnicity, and geographic region was used to calculate odds ratios; reference categories for binary variables were those without the characteristic. Missing data at initiation of renal replacement therapy: eGFR, 0.5%; body mass index, 3.0%; serum albumin, 24.8%; hemoglobin, 9.4%.
[a] $P \geq 0.05$.
[b] $0.01 \leq P < 0.05$.
[c] $0.001 \leq P < 0.01$.
$P < 0.001$ unless otherwise indicated.

(n = 2385 total). ESKD from scleroderma declined in the United States over the years of observation (Figure 1, Table 1), with adjusted incidence ratios (AIRs) falling to 0.42 by 2012 (vs. 1996, 95% confidence interval [CI] = 0.32–0.54, $P < 0.001$). Other associations included the following: age, peaking at 65 to 79 years (AIR = 1.61, vs. 40–64 years, 95% CI = 1.47–1.76, $P < 0.001$); female sex (AIR = 2.83, 95% CI = 2.58–3.11, $P < 0.001$); African American/black race (AIR = 1.84, vs. white, 95% CI = 1.65–2.04, $P < 0.001$); and residence in southern states (AIR = 0.84, vs. northeastern states, 95% CI = 0.75–0.94, $P < 0.01$). Calendar year–associated AIR values fell in every subgroup examined, except age < 20 years and Asian race (Table 1).

Factors associated with a greater likelihood of scleroderma than other causes of ESKD at initiation of RRT included female sex (adjusted odds ratio [AOR] = 4.13, 95% CI = 3.76–4.54, $P < 0.001$) and serum albumin < 3.5 g/dl (AOR = 1.42, 95% CI = 1.29–1.58, $P < 0.001$) (Table 2); factors associated with a lower likelihood of scleroderma included more recent era (AOR = 0.53 for 2006–2012 vs. 1996–2000, 95% CI = 0.48–0.59, $P < 0.001$), older age (AOR = 0.15 for age ≥ 80 years, vs. < 40 years, 95% CI = 0.48–0.59,

Table 3. Adjusted hazards ratios for outcomes in patients with scleroderma (scleroderma$^+$) and in matched patients without scleroderma

Event of interest within each follow-up period	Rate, scleroderma$^+$	Hazard ratios for scleroderma (yes vs. no)
Followed from initiation of renal replacement therapy		
(2398 pairs, mean follow-up 3.3 yr)		
Death	22.0 (21.0–23.1)	1.44 (1.34–1.54)
Listing for transplant	1.5 (1.3–1.8)	0.80 (0.64–1.00)[a]
Transplantation	3.6 (3.2–4.1)	0.51 (0.44–0.59)
Deceased-donor transplant	1.9 (1.6–2.3)	0.47 (0.39–0.58)
Living-donor transplant	1.7 (1.4–2.1)	0.56 (0.45–0.69)
Recovery	1.6 (1.3–1.9)	2.67 (1.90–3.76)
Followed from listing for transplant		
(392 pairs, mean follow-up 5.0 yr)		
Death	8.6 (7.4–9.9)	1.23 (0.98–1.53)[a]
Transplantation	21.9 (19.0–25.1)	0.65 (0.54–0.78)
Deceased-donor transplant	13.2 (11.1–15.8)	0.75 (0.59–0.96)[b]
Living-donor transplant	8.6 (6.9–10.8)	0.54 (0.41–0.71)
Followed from transplant		
(260 pairs, mean follow-up 5.4 yr)		
Death	6.4 (5.2–7.9)	0.97 (0.73–1.29)[a]
Graft failure	1.2 (0.4–3.8)	0.90 (0.85–0.95)

[a] $P \geq 0.05$.
[b] $0.01 \leq P < 0.05$.
Rates are reported per hundred person-years. Ninety-five percent confidence intervals are shown in parentheses. Factors used for matching were calendar year, age, sex, race, ethnicity, and region.
$P < 0.001$ unless otherwise indicated.

$P < 0.001$), African American/black race (AOR = 0.41, vs. white, 95% CI = 0.37−0.46, $P < 0.001$), Hispanic ethnicity (AOR = 0.43, 95% CI = 0.36−0.50, $P < 0.001$), residence outside the northeastern states, peritoneal dialysis (AOR = 0.64, vs. hemodialysis, 95% CI = 0.54−0.75, $P < 0.001$), transplant (AOR = 0.21, vs. hemodialysis, 95% CI = 0.13−0.34, $P < 0.001$), vascular disease (AOR = 0.49, 95% CI = 0.44−0.54, $P < 0.001$), diabetes (AOR = 0.07, 95% CI = 0.06−0.08, $P < 0.001$), malignancy (AOR = 0.58, 95% CI = 0.46−0.73, $P < 0.001$), and body mass index > 30 kg/m^2 (AOR = 0.15, 95% CI = 0.13−0.17, $P < 0.001$) (Table 1).

Compared to demography-matched patients without scleroderma, those with scleroderma were more likely to die (hazards ratio [HR] = 1.44, CI = 1.34−1.54, $P < 0.001$) and recover kidney function (HR = 2.67, CI 1.90−3.76, $P < 0.001$) and less likely to receive a transplant (HR = 0.51, CI = 0.44−0.59, $P < 0.001$) after initiating RRT (Table 3, Figure 2); after transplantation, scleroderma was associated with a lower likelihood of graft failure (HR = 0.90, CI = 0.85−0.95, $P < 0.001$). Scleroderma-specific risk factors for death, recovery, listing, transplantation, and graft failure are shown in Supplementary Table S1. Further comparisons of outcomes between scleroderma and other primary diseases are detailed in Supplementary Table S2.

DISCUSSION

We found that the incidence of ESKD from scleroderma declined during the 16-year interval of observation. The burden of ESKD fell in individuals of both sexes, and in all but 1 race/ethnicity category and 1 age group. Although it is tempting to hypothesize that the encouraging trends in scleroderma-related RRT may reflect improvements in the management of scleroderma, the nonexperimental design of our study does not allow us to make such an inference.

Possible explanations for these salutary trends might include a combination of improvements in overall management, despite the lack of specific therapies, such as the widespread use of angiotensin-converting enzyme inhibitors and/or calcium channel blockers and directed therapy for scleroderma-related vascular phenomena such as pulmonary arterial hypertension, Raynaud phenomenon, and digital ulceration.[8,13,14,17–21] Although the incidence of scleroderma renal crisis itself is also thought to be falling, the impact of this on ESKD may theoretically be counterbalanced by improving survival, with mortality falling from approximately 76% at 1 year

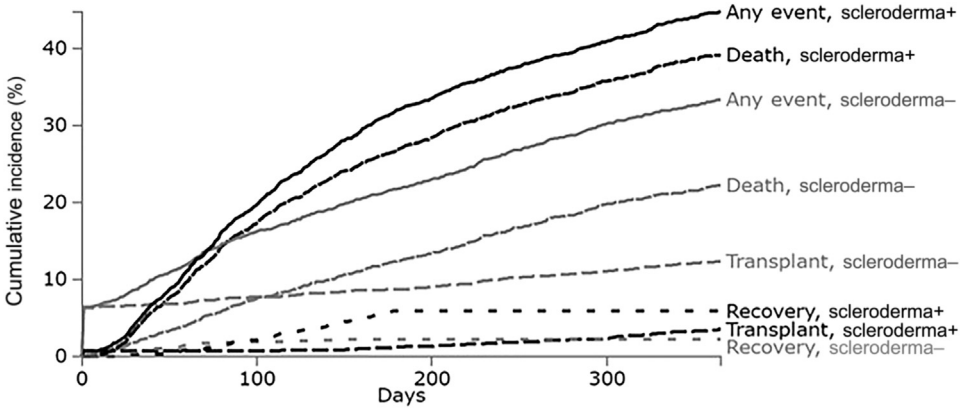

Figure 2. Cumulative incidence of the following events in patients starting renal replacement therapy with scleroderma (n = 2398) and matched patients without scleroderma (n = 2398) in an analytical framework in which all clinical events are competing with each other: death, transplantation, recovery of kidney function, or any of these events.

initially to less than 10% following the introduction of angiotensin-converting enzyme inhibitor use in scleroderma renal crisis.[12]

There are other possible explanations for these observed trends, such as a reduced incidence of scleroderma in the general population, an increased mortality as a competing risk for ESKD among individuals with scleroderma, or a failure to capture ESKD cases not treated with dialysis or transplantation.[22] As with other uncommon conditions with variable severity and presentation, an accurate assessment of incidence is difficult, because precise identification of first disease onset may be difficult.[12,23,24] Although mortality rates in scleroderma, both overall and in renal crisis, are thought to be falling, the incidence of scleroderma, as of 2008, was thought to be stable, which may make the salutary trends in ESKD seen even more noteworthy, as one might expect an increase in incidence in this setting.[12,23,24]

Although more likely in scleroderma cases than in matched patients without scleroderma, recovery of dialysis independence was still relatively uncommon, and appeared to occur relatively early after dialysis initiation. Our findings regarding renal recovery are similar to a previous report from the ANZDATA registry.[25] Although we found that mortality risk in the contemporary era remains high for ESKD patients with scleroderma in comparison to other causes, the mortality disparity was not evident after renal transplant.[12,19,23] Scleroderma is thought to be more common in African Americans, and we did find a higher rate of ESKD associated with African American/black race, along with a lower likelihood of listing for transplantation and receiving a renal transplant. The reasons for this are unclear but possibly relate to disease-specific factors in African American/black race, as well as possible racial heterogeneity in access to medical care in the United States.[21,24,26] The findings pertaining to renal transplantation in scleroderma may be encouraging and consistent with the available literature, which, although limited, suggests a survival benefit to renal transplantation in scleroderma.[27,28]

This study has several limitations, including retrospective registry-based design and a lack of information about earlier stage kidney disease and treatments received. The agreement between the primary diagnosis as presented on Form 2728 and biopsy-proven disease has been questioned for glomerulonephritis.[29] In USRDS-based studies the generalizability of findings to different primary diseases may be limited by this fact. Although the diagnosis of scleroderma is often made clinically without tissue biopsy, we cannot refute the possibility that there may be some misclassification bias inherent to the USRDS dataset. Inability to identify participants who initiate RRT for acute kidney injury from scleroderma, and uncertainty about discriminating irreversible ESKD from reversible acute kidney injury, is a limitation of dialysis patient registries, in which information starts to accrue only after kidney disease is labeled as irreversible. Finally, matching for comparison of outcomes could conceivably have introduced unknown confounding.

Despite its limitations, we feel that our study provides some useful information. Although research efforts to develop alternative efficacious treatments are clearly needed, it is encouraging that rates of RRT from scleroderma appear to be declining. The reduction in the incidence of ESKD from scleroderma identified in this study, synchronous with the reduction in mortality in scleroderma reported in prior studies, is encouraging.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government. The Health Research Board of Ireland funded DS.

SUPPLEMENTARY MATERIAL

Table S1. Adjusted hazards ratios for outcomes of renal replacement therapy in patients with scleroderma.

Table S2. Adjusted hazards ratios for outcomes in patients with scleroderma and in matched patients without scleroderma.

Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum*. 1998;41:778–799.
2. Nihtyanova SI, Tang EC, Coghlan JG, et al. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. *Q J Med*. 2010;103:109–115.
3. Penn H, Howie AJ, Kingdon EJ, et al. Scleroderma renal crisis: patient characteristics and long-term outcomes. *Q J Med*. 2007;100:485–494.
4. Cozzi F, Marson P, Cardarelli S, et al. Prognosis of scleroderma renal crisis: a long-term observational study. *Nephrol Dial Transplant*. 2012;27:4398–4403.
5. Guillevin L, Berezne A, Seror R, et al. Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. *Rheumatology [Oxford]*. 2012;51:460–467.

6. Kingdon EJ, Knight CJ, Dustan K, et al. Calculated glomerular filtration rate is a useful screening tool to identify scleroderma patients with renal impairment. *Rheumatology [Oxford]*. 2003;42:26–33.
7. Campo A, Mathai SC, Le Pavec J, et al. Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2010;182:252–260.
8. Damman K, van Deursen VM, Navis G, et al. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol*. 2009;53:582–588.
9. Locke IC, Worrall JG, Leaker B, et al. Autoantibodies to myeloperoxidase in systemic sclerosis. *J Rheumatol*. 1997;24:86–89.
10. Wielosz E, Dryglewska M, Majdan M. Antiphospholipid antibodies and kidney involvement in patients with systemic sclerosis. *Clin Rheumatol*. 2009;28:955–959.
11. Hall CL, Jawad S, Harrison PR, et al. Natural course of penicillamine nephropathy: a long term study of 33 patients. *Br Med J [Clin Res Ed]*. 1988;296:1083–1086.
12. Steen VD, Costantino JP, Shapiro AP, et al. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann Intern Med*. 1990;113:352–357.
13. Fischer A, Bull TM, Steen VD. Practical approach to screening for scleroderma-associated pulmonary arterial hypertension. *Arthritis Care Res [Hoboken]*. 2012;64:303–310.
14. Rao V, Bowman S. Latest advances in connective tissue disorders. *Ther Adv Musculoskelet Dis*. 2013;5:234–249.
15. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
16. Fine JPGR. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
17. Shanmugam VK, Steen VD. Renal disease in scleroderma: an update on evaluation, risk stratification, pathogenesis and management. *Curr Opin Rheumatol*. 2012;24:669–676.
18. Muangchan C, Canadian Scleroderma Research G, Baron M, et al. The 15% rule in scleroderma: the frequency of severe organ complications in systemic sclerosis. A systematic review. *J Rheumatol*. 2013;40:1545–1556.
19. Abbott KC, Trespalacios FC, Welch PG, et al. Scleroderma at end stage renal disease in the United States: patient characteristics and survival. *J Nephrol*. 2002;15:236–240.
20. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis*. 2010;69:1809–1815.
21. Mendoza F, Derk CT. Systemic sclerosis mortality in the United States: 1999–2002 implications for patient care. *J Clin Rheumatol*. 2007;13:187–192.
22. Rebholz CM, Coresh J, Ballew SH, et al. Kidney failure and ESRD in the Atherosclerosis Risk in Communities (ARIC) Study: comparing ascertainment of treated and untreated kidney failure in a cohort study. *Am J Kidney Dis*. 2015;66:231–239.
23. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis*. 2007;66:940–944.
24. Chifflot H, Fautrel B, Sordet C, et al. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum*. 2008;37:223–235.
25. Siva BMS, Hawley CM, Rosman J, Brown FG, Wiggins KJ, Bannister KM, Campbell SB, Johnson DW. End-stage kidney disease due to scleroderma–outcomes in 127 consecutive ANZDATA registry cases. *Nephrol Dial Transplant*. 2011;26:3165–3171.
26. US Census Bureau. State intercensal estimates (2000–2010). Available at: https://www.census.gov/2010census/data. Accessed June 2016.
27. Trang G, Steele R, Baron M, et al. Corticosteroids and the risk of scleroderma renal crisis: a systematic review. *Rheumatol Int*. 2012;32:645–653.
28. Gibney EM, Parikh CR, Jani A, et al. Kidney transplantation for systemic sclerosis improves survival and may modulate disease activity. *Am J Transplant*. 2004;4:2027–2031.
29. Layton JB, Hogan SL, Jennette CE, et al. Discrepancy between Medical Evidence Form 2728 and renal biopsy for glomerular diseases. *Clin J Am Soc Nephrol*. 2010;5:2046–2052.