Trends in mortality rates on hemodialysis in Canada, 1981–1997

DOUGLAS E. SCHAUBEL and STANLEY S.A. FENTON

Department of Biostatistics, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; Faculty of Medicine, University of Toronto, Toronto; Division of Nephrology, Toronto General Hospital, Toronto; University Health Network, Toronto, Ontario, Canada

Trends in mortality rates on hemodialysis in Canada, 1981-1997. Significant improvements in hemodialysis (HD) have occurred during recent years. Few previous studies have explicitly examined trends in patient outcomes over time. In order to evaluate whether improvements in HD have resulted in decreased mortality, we analyzed trends in mortality rates among the 28,700 patients who initiated HD in Canada during the 1981-1997 period. Mortality rate ratios (RR) were estimated using Poisson regression, and adjusted simultaneously for age, race, gender, primary renal diagnosis and follow-up time. Adjusted mortality rates decreased significantly by calendar period, with RR = 0.90 (95% CI: 0.83-0.96) for 1990-93 and RR = 0.74 (0.69-0.80)for 1994–97, relative to 1981–85 (reference; RR = 1). The decrease was concentrated in the first two years of follow-up. Among causes of death, mortality due to cardiovascular disease showed the sharpest decline. Among subgroups defined by age and diabetes status, mortality improvement was strongest among diabetics age <65 years and weakest among non-diabetics age <65 years. The observed decreases in HD mortality could be due to enhancements in dialysis technology, including improvements in dialysis machines, water purification systems, dialysate composition, and biocompatibility of dialyzer membranes. Key roles were likely played by increased attention to HD adequacy on the part of clinicians, improved nutrition, better management of comorbid conditions, and increased erythropoietin utilization. Detailed data on practice patterns are required in order that the degree of association between trends in dialysis methodology and mortality may be quantitatively evaluated.

Significant enhancements to hemodialysis (HD) have occurred since the initial development of the technique [1], and particularly in recent years [2]. Due to increased attention to dialysis adequacy, the average dose of dialysis has increased [3–6]. Major advances have occurred in membrane technology, as dialyzers with greater biocompatibility, greater flux and higher clearance rates have been developed [7–10]. Erythropoietin was introduced to combat anemia [11, 12], while bicarbonate replaced acetate as the dialysate most commonly employed [13].

Despite such major changes in HD methods and prac-

tices, few previous studies have explicitly examined trends over time in patient outcomes [14–17]. In order to assess whether the above-listed improvements in HD have, in aggregate, resulted in improved survival, we analyzed trends in mortality rates among Canadian end-stage renal disease (ESRD) patients receiving HD during the 1981–1997 period.

METHODS

Data for all patients initiating therapy between January 1, 1981 and December 31, 1997 were obtained from the Canadian Organ Replacement Register (CORR) of the Canadian Institute for Health Information (CIHI). CORR is a population-based, nation-wide organ failure registry [18]. Coverage is complete in the sense that patient records are submitted annually by each of the 86 renal Canadian centers. Demographic data recorded at the time of initiation of renal replacement therapy (RRT) include date of birth, gender, province of residence, race, predialysis comorbid conditions, and primary renal diagnosis (PRD). RRT data are submitted annually by each center, including dialytic modality switches, transplantations, and graft failures. Where applicable, date and cause of death is reported along with the other follow-up data.

Included were all ESRD patients who received HD at some time between January 1, 1981 and December 31, 1997, the start and conclusion of the period of observation, respectively. Patients were classified by gender, PRD, and race (Black, Caucasian, First Nations, Oriental, Asian Indian, Other). Follow-up time on hemodialysis was computed for each patient, with person-years (PY) of follow-up classified by age (≤ 14 , 15–44, 45–64, $65-74, \geq 75$), calendar period (1981–1985, 1986–1989, 1990–1993, 1994–1997), and follow-up time (1-year intervals). Naturally, age, calendar period, and follow-up interval were dynamic variables in that patients could contribute PYs to more than one category, as they were followed longitudinally through the period of observation. Hence, our analysis accounted for the migration of patients through age, calendar period and follow-up time

Key words: dialysis, end-stage renal disease, epidemiology, renal failure, survival.

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categories. Patients who received a kidney transplant were censored at the date of transplantation.

Mortality rates were computed as the ratio of deaths to person-time within each cross-classification defined by age, sex, race, follow-up time window and calendar period. Deaths were allocated to the dialytic modality received at the time of death. That is, deaths were only counted against HD if the patient was receiving HD at the time of death. Poisson regression [19, 20] was used to compare calendar-period-specific mortality rates while adjusting simultaneously for all previously listed covariables. That is, the logarithm (base e) of the mortality rate was modeled as a linear function of parameters representing each variable. The mortality rate ratio (RR, i.e., death rate for each calendar period, relative to the arbitrarily chosen reference period: 1981–1984) served as the parameter of interest.

In terms of supplementary analysis, separate Poisson regression models were fitted by age and diabetes status in order to examine the consistency of the trend in adjusted mortality rates across patient subpopulations. Follow-up time window-specific models were also fitted. Trends over time for major causes of death (COD) were examined to assess the degree of uniformity in CODspecific trends, and in order to add context to observed trends in all-cause mortality. A model was also fitted with both "calendar period" and "cohort" variables, for the purpose of determining whether the trends in mortality rates were strongest cross-sectionally across calendar time or longitudinally within patient cohorts. Trends in transplant rates among HD patients were also evaluated in order to further assess changes in the HD case-mix.

RESULTS

In Table 1, baseline characteristics are presented for the 28,700 patients who received hemodialysis at some time between 1981 and 1997. Approximately 38% of the HD population initiated HD after age 65 years, while about 1% of patients were children aged 14 years and under. The male : female split was approximately 61 : 39. The majority of patients were Caucasian (79%), while First Nations patients comprised 5% of the HD population. Approximately 22% of patients were diabetic. The number of patients initiating HD increased greatly during our period of observation. During the most recent calendar period, 1994–1997, slightly over 11,000 patients began HD.

The hemodialysis patient age and PRD distributions by calendar period are displayed in Table 2. The percentage of patients in each age group decreased over calendar time, with the exception of the \geq 65 years category. The fraction of patients in the 15–44 years age group was reduced by one half during 1994–1997 compared to 1981– 1985, while the percentage in the \geq 65 years age group

Table 1.	Baseline characteristics of patients initiating hemodialy	sis
	in Canada during 1981–1997	

Characteristic ^a	Ν	% ^b
Age group		
≤14	327	1.1
15-44	6917	24.1
45-64	10,450	36.4
≥65	11,006	38.3
Gender		
Female	11,107	38.7
Male	17,589	61.3
Unknown	4	0.0
Race		
Asian Indian	514	1.8
Black	634	2.2
Caucasian	22,674	79.0
First Nations	1313	4.6
Oriental	1086	3.8
Other	2479	8.6
Calendar period		
1981–1985	4460	15.5
1986–1989	5555	19.4
1990–1993	7678	26.8
1994–1997	11,007	38.4
Primary renal diagnosis		
Diabetes mellitus	6199	21.6
Glomerulonephritis	4731	16.5
Polycystic kidney disease	1690	5.9
Renal vascular disease	4849	16.9
Other	11,231	39.1
Total	28,700	100

^aPatients classified based on date of renal replacement therapy initiation ^bPercentages may not add to 100 due to rounding

experienced a greater than two-fold increase. Correspondingly, the mean age at HD-initiation increased steadily over time, from 49.2 in 1981–1985 to 59.5 in 1994–1997. The percentage of patients with diabetes as a PRD more than doubled during the period of observation, while that for glomerulonephritis reduced by greater than one half.

In total, we observed 10,685 deaths on hemodialysis during a total of 52,583 person-years, for an overall mortality rate of 203.2 per 1000 PY (Table 3). Unadjusted mortality RRs were significantly increased for 1986–1989, 1990–1993 and 1994–1997 relative to 1981–1985. However, a strong monotone decreasing trend was observed with respect to the covariable-adjusted mortality RRs. Significant reductions were witnessed for the 1990–1993 (RR = 0.90; 95% CI: 0.83–0.96) and 1994–1997 (RR = 0.74; 0.69–0.80) calendar periods relative to 1981–1985.

A more detailed examination of the trend in adjusted HD patient mortality is depicted in Fig. 1. Here, 8 calendar periods are employed, with 1981–1983 serving as the reference and the remainder of the observation period broken into 2-year intervals. The improvement in HD mortality does not appear to level off. In fact, the decline in RR, steady between 1984 and 1995, strengthens appreciably during the 1995–1996 period.

Covariable-adjusted mortality rate ratios are pre-

Table 2. Distribution ^a by age and primary renal diagnosis for patients initiating hemodialysis in Canada, 1981–199	Table 2.	Distribution ^a by ag	e and primary renal	diagnosis for	patients initiating	hemodialysis in	Canada, 1981-1997
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Characteristic ^b	1981–1985	1986–1989	1990–1993	1994–1997
Age group				
≤14	2	1	1	1
15-44	36	28	22	18
45-64	41	38	36	34
≥65	22	32	40	47
Mean age (years)	49.2	53.7	56.8	59.5
Primary renal diagnosis				
Diabetes	13	18	22	27
Glomerulonephritis	27	19	15	12
Polycystic kidneys	8	7	6	5
Vascular	13	15	18	19
Other	41	41	39	38

^aDistribution is expressed in percent. Percentages may not add to 100 due to rounding

^bAt date of renal replacement therapy initiation

Table 3. Hemodialysis mortality rates and rate ratios by calendar period

Calendar			Unadjusted	Unadjusted		А	djusted ^c
period	Deaths	PY	rate per 1000	RR ^a	95% CI ^b	RR	95% CI
1981–1985	941	5259	178.9	1	_	1	_
1986-1989	1953	9581	203.8	1.14	1.03-1.25	0.95	0.88-1.03
1990-1993	3178	14,614	217.5	1.22	1.11-1.33	0.90	0.83-0.96
1994-1997	4613	23,129	199.5	1.11	1.02-1.22	0.74	0.69-0.80
1981–1997	10,685	52,583	203.2				

 $^{a}RR = mortality rate ratio$

^bCI = confidence interval

°RR estimated using Poisson regression, and adjusted for age, gender, race, primary renal diagnosis and follow-up time

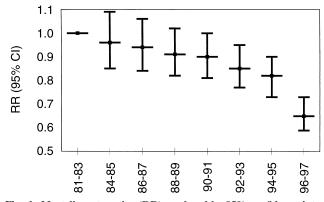


Fig. 1. Mortality rate ratios (RR), enclosed by 95% confidence intervals (CI) for hemodialysis patients in Canada, 1981–1997. Calendar time was divided into 8 subintervals, with 1981–1983 serving as the reference period (RR = 1, fixed). RRs were estimated using Poisson regression, and adjusted for age, gender, race, primary renal diagnosis and follow-up time.

Table 4. Adjusted hemodialysis mortality rate ratios by ca	alendar
period and patient subpopulation	

Patient subpopulation	Calendar period	RR^{a}	95% CI ^b
Non-diabetics	1981-1985	1	_
Age <65	1986-1989	1.01	0.91-1.13
0	1990-1993	1.01	0.91-1.12
	1994–1997	0.88	0.79-0.98
Non-diabetics	1981-1985	1	_
Age ≥ 65	1986-1989	0.88	0.78 - 1.00
0	1990-1993	0.83	0.74-0.93
	1994–1997	0.70	0.63-0.79
Diabetics	1981-1985	1	_
Age <65	1986-1989	0.81	0.64 - 1.02
0	1990-1993	0.73	0.59-0.91
	1994–1997	0.54	0.44-0.67
Diabetics	1981-1985	1	_
Age ≥ 65	1986-1989	1.02	0.72-1.46
C	1990-1993	0.81	0.58-1.14
	1994–1997	0.65	0.47-0.91

 ${}^{a}RR =$ rate ratio, estimated using Poisson regression and adjusted for age, gender, race, primary renal diagnosis, and follow-up time ${}^{b}CI =$ confidence interval

sented by age and diabetes status in Table 4. The strongest gradient of decrease was experienced by diabetics aged <65 years, with 1994–1997 adjusted mortality rates being reduced by 46% relative to 1981–1985. For nondiabetics aged <65 years and diabetics aged <65 years, the decrease in adjusted mortality rates was statistically significant for the two most recent calendar periods. For

non-diabetics aged <65 years and diabetics aged \geq 65 years, the mortality reduction attained statistical significance only for the 1994–1997 calendar period. Literally no decrease in adjusted death rates was observed during 1986–1989 and 1990–1993 (RR \approx 1 for each) among non-

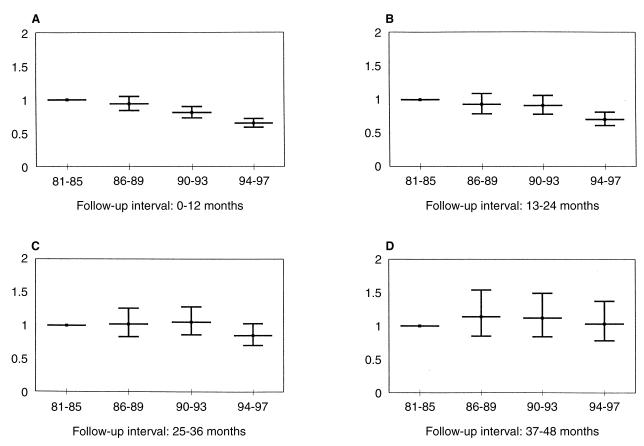


Fig. 2. Mortality rate ratios (RR) and 95% confidence intervals (CI) for hemodialysis patients by follow-up time interval in Canada, 1981–1997. Calendar time was divided into 4 subintervals, with the 1981–1985 period serving as the reference (RR = 1, fixed). Each panel pertains to a separate time window following initiation of renal replacement therapy. RRs were estimated using Poisson regression, and adjusted for age, gender, race, primary renal diagnosis.

diabetics aged <65 years. Within the diabetic/ ≥ 65 years category, statistical power is limited, as evidenced by the width of the confidence intervals.

Adjusted rate ratios are displayed by follow-up time in Fig. 2. A steady decline in mortality was observed during the first year post-initiation of RRT, with RRs significantly reduced for the 1990–1993 and 1994–1997 calendar periods (Fig. 2A). In follow-up year two, little change in mortality occurred for the first two calendar periods, although a significantly reduction was observed for 1994–1997. During year 3, the decrease in RR barely failed to reach significance for 1994–1997 and was absent for earlier periods (Fig. 2C). No discernible trend in mortality was observed during the fourth year of followup (Fig. 2D).

The cause-of-death distribution is listed by calendar period in Table 5. Within each period, cardiovascular disease (CVD) was the most frequent COD, the percentage falling slightly from 41% in 1981–85–36% during 1994–97. Generally, the distribution of deaths by COD was quite stable over time. However, the percentage of deaths due to social causes (e.g., suicide, refusal to

 Table 5. Distribution of causes of death by calendar period in Canadian hemodialysis patients, 1981–1997^a

Cause of death	1981–1985	1986–1989	1990–1993	1994–1997
CVD ^b	41	40	39	36
Infection	9	9	9	8
Vascular	7	7	6	7
Social	10	14	16	19
Other/unspecified	33	30	31	29

^aDistribution is expressed as a percent

^bCVD = cardiovascular disease

continue therapy) increased greatly, from 10% in 1981–1985 to 19% during 1994–1997.

COD–specific adjusted mortality rate ratios are listed in Table 6. The strongest decrease was observed for deaths due to CVD, which accounted for 38% of the total number of deaths. Strong decreases also occurred with respect to deaths due to infection and vascular disorders. During the 1994–1997 period, RRs were significantly decreased for each COD category, with the exception of deaths due to social causes, which showed a significant increase for all periods subsequent to 1981–1985.

Cause of death	Ν	%	1981–1985 RR (95% CI)	1986–1989 RR (95% CI)	1990–1993 RR (95% CI)	1994–1997 RR (95% CI)
CVD ^a	4073	38.1	1	0.91 (0.82, 1.00)	0.81 (0.73, 0.89)	0.62 (0.56, 0.68)
Infection	933	8.7	1	(0.82, 1.00) 0.94 (0.80, 1.10)	(0.79, 0.09) 0.92 (0.79, 1.07)	(0.50, 0.00) 0.78 (0.67, 0.90)
Vascular	725	6.8	1	(0.30, 1.10) 0.89 (0.75, 1.04)	(0.73, 1.07) 0.80 (0.68, 0.93)	(0.67, 0.90) 0.78 (0.68, 0.91)
Social ^b	1737	16.3	1	1.24	(0.08, 0.93) 1.27 (1.10, 1.46)	1.20
Other/unspecified	3217	30.1	1	(1.07, 1.44) 0.87 (0.78, 0.08)	0.88	(1.05, 1.38) 0.72 (0.65, 0.80)
All causes	10,685	100	1	(0.78, 0.98) 0.95 (0.88, 1.03)	(0.79, 0.97) 0.90 (0.83, 0.96)	(0.65, 0.80) 0.74 (0.69, 0.80)

Table 6. Hemodialysis mortality rate ratios for selected causes of death (COD) by calendar period

^aCVD is cardiovascular disease

^bSuicide, refusal to continue therapy, etc

Table 7. Adjusted mortality rate ratios by patient cohort and calendar period hemodialysis patients in Canada, 1981–1997

RR⁰	95% CI ^c	Calendar period ^a	RR^{b}	95% CI ^c
1	_	1981-1985	1	_
1.10	1.03-1.18	1986-1989	0.89	0.82-0.97
1.12	1.04-1.21	1990-1993	0.81	0.73-0.88
0.96	0.88 - 1.15	1994–1997	0.71	0.64 - 0.79
	1 1.10 1.12	4	1 — 1981–1985 1.10 1.03–1.18 1986–1989 1.12 1.04–1.21 1990–1993	1 — 1981–1985 1 1.10 1.03–1.18 1986–1989 0.89 1.12 1.04–1.21 1990–1993 0.81

^aPatients classified based on date of initiation of HD

 ${}^{b}RR$ = rate ratio, estimated using Poisson regression and adjusted for age, gender, race, primary renal diagnosis, and follow-up time

^cCI = confidence interval

In Table 7, results are presented for a regression model that contained terms for calendar time in the "period" and "cohort" sense. The cohort variable was defined once, and only once, per patient, and represents the calendar time interval during which HD was initiated. As stated, patients could contribute PYs to more than one calendar "period" variable during their follow-up time. Only the "period" RRs indicate significant decreases in adjusted mortality.

Results in Table 8 pertain to a regression model where transplantation replaced death as the end-point of interest. Only first renal transplants were included. Relative to 1981–1985, covariable-adjusted transplant rates were significantly increased during the 1986–1989 period (RR = 1.17). However, significant decreases were observed during 1990–1993 (RR = 0.86) and 1994–1997 (RR = 0.70). There was great discrepancy between the unadjusted and covariable-adjusted RRs in terms of magnitude and, for 1986–89, direction.

DISCUSSION

We observed a statistically significant decrease in hemodialysis mortality rates in Canada during the 1981– 1997 period, after adjustment for age, gender, race, primary renal diagnosis and follow-up time. The decline did not show signs of leveling off, and appears to have increased for more recent calendar periods. The improvement was concentrated within the first year of follow-up. Among causes of death, the improvement in mortality was strongest for CVD-attributable deaths. Among patient subpopulations, the mortality decrease was most pronounced for diabetics aged <65 years, and least pronounced for non-diabetics aged <65 years.

The decrease in HD mortality is likely related to technical and therapeutic advances in HD that took place during the period of observation. In terms of equipment, the sophistication of dialysis machines continues to increase over time. Membranes have been developed which are more biocompatible, while high-efficiency and high-flux dialyzers permit elevated rates of clearance [7–10]. A shift from acetate to bicarbonate dialysate has also occurred [13]. Increased attention has been accorded to dialysis adequacy, which has led to increases in the average dose of dialysis [3–6], and ultimately to the formal establishment of guidelines of HD care [21]. Based on data from the United States Renal Data System (USRDS) [22], it has also been hypothesized that patients are now initiating RRT earlier in the disease process than in the past [23]. Nutrition and the management of comorbid illnesses have also improved. Each of the above-listed factors has been found to influence patient outcomes to various degrees. The extent to which each of these factors is associated with the decline in HD mortality is unclear since data on practice patterns among Canadian nephrologists is sparse.

Few studies have explicitly evaluated mortality trends for HD or other RRTs. Based on data from the Michigan Kidney Registry (MKR), Wolfe et al reported that incenter HD adjusted log (death rates) experienced a significant 6% average annual increase between 1980 and 1987 [14]. In a subsequent study also based on MKR data, Nelson et al found an increase of 4% per year (P <0.06) in adjusted log (RR) among HD patients during the 1980–1989 period [15]. However, the Morbidity,

			Unadjusted	Unadjusted		А	djusted ^d
Calendar period	Kidney ^a transplants	Person-years	rate per 1000	RR ^b	95% CI°	RR	95% CI
1981-1985	1,153	5,259	219.2	1	_	1	_
1986-1989	1,799	9,581	187.8	0.86	0.78-0.94	1.17	1.10-1.24
1990-1993	1,655	14,614	113.5	0.52	0.47 - 0.57	0.86	0.81-0.92
1994-1997	1,797	23,129	77.7	0.35	0.32-0.39	0.70	0.66-0.75
1981-1997	6,404	52,583	121.8				

Table 8. Adjusted transplantation^a rate ratios for hemodialysis patients by calendar period

^a Only first renal transplants were included

 $^{b}RR = transplant rate ratio$

^cRR estimated using Poisson regression and adjusted for age, gender, race, primary renal diagnosis, and follow-up time

 d CI = confidence interval

Mortality and Prescription of Dialysis Symposium [24] dramatically altered HD prescription practices in the U.S. and elsewhere. Correspondingly, more recent data from the U.S. are more encouraging. Based on the USRDS database, Wolfe et al [16] and Port et al [17] observed significant reductions in first- and second-year HD mortality rates between 1985 and 1995. Similar to the current investigation, the USRDS results indicate that the improvement in mortality is stronger in year 1 than in year 2 of follow-up. Unlike our study, Port et al [17] had available data on various treatment parameters, including dialysis dose, treatment time, membrane type and dialysate buffer. The authors report increases in average dialysis dose, use of synthetic membranes and use of bicarbonate dialysate, and attribute the majority of the mortality reduction to changes in dose and dialysate.

Registry data are invaluable in the context of examining trends in outcomes over calendar time, since the cost of following a sufficient number of patients over a sufficiently long time period to discern meaningful trends would clearly be prohibitive. However, registry data do suffer some liabilities. Although the Registry is complete in the sense that all patient records are forwarded by all Canadian renal centers, data are not validated or audited. However, it is extremely doubtful that data quality differed between calendar periods in such a way as to bias our results. Comorbidity data were available, but not utilized since they were only collected for patients initiating RRT from 1988 onward. If anything, this would be expected to result in under-estimation of the improvement in mortality. That is, since we find no decrease in unadjusted mortality, but observe a significant decrease upon adjustment for available covariables, one would expect that more refined adjustment would, if anything, produce an even stronger effect. When models were fitted based on only patients from 1988 to 1996, calendar time RRs were similar when adjusted, and not adjusted, for comorbidity (data not shown). Although the comorbidity profile for patients would be expected to worsen with calendar time, the worsening is, likely, largely captured by age and PRD.

Rates of HD mortality due to social causes, unlike

any other COD category, were significantly increased for each calendar period subsequent to 1981–1985. Subgroup analysis revealed that HD mortality did not significantly decrease among nondiabetic patients aged <65 years. It is noteworthy that this subgroup, unlike all others, experienced significantly increased adjusted rates of death due to social causes during the 1986–1989 (RR = 1.84), 1990–1993 (RR = 2.24) and 1994–1997 (RR = 2.11) calendar periods (data not tabulated). In fact, RRs for deaths due to social causes were increased, albeit much less dramatically, among non-diabetics aged \geq 65 years, while decreasing trends were observed for diabetics (data not shown). Explanations for such results are unavailable, and warrant future study.

Another recent investigation based on the CORR database examined trends in mortality on peritoneal dialysis (PD) [25]. Generally, findings were similar in that significant decreases were observed for adjusted PD mortality. Among CODs, the overall improvement was mostly driven by CVD mortality. As well, the effect was concentrated early in the follow-up period. However, the HD and PD results differed in a few important ways. Although diabetics aged <65 years experienced the greatest mortality decrease over time, no appreciable difference in the mortality trends by patient subpopulation was observed. For PD, no increase in rates of death due to social causes were observed. Although mean age and diabetes prevalence increased over time for both the HD and PD studies, unlike the current results, the unadjusted mortality RRs were comparable to the covariable-adjusted RRs in the PD study.

In both the HD and PD studies, rates of outcomes other than death were considered as possible explanations for the decreasing mortality trend. Since technique failure and transplantation could "compete" against mortality in such a way that artificial improvements in mortality appear, much attention in the PD study was directed towards evaluating trends in other forms of transfer from PD (i.e., technique failure, transplantation). Transplant rates were, actually, increased, while a decreasing trend in technique failure rates was observed, thus eliminating both as potential sources of bias. Upon more detailed examination, technique failure RRs for CAPD alone were found to be significantly reduced during the 1990s relative to the 1980s (Schaubel et al, manuscript in preparation). Naturally, due to its rarity, HD technique failure would not be expected to induce bias in observed mortality trends. However, unlike PD, transplant rates from HD were significantly decreased for both the 1990-1993 and 1994-1997 periods. Analysis of the correspondence between HD death and transplant trends offer further evidence of their association. For example, the patient subgroup experiencing the greatest decrease in mortality RRs (i.e., diabetics aged <65 years) also experienced the greatest decrease in transplant RRs (e.g., RR = 0.35 (0.28, 0.43) during 1994–1997 relative to 1981–1985; data not tabulated). When transplant rates are decreased, concern arises that healthier patients remain on dialysis (i.e., who would have been transplanted in a previous calendar period when the donor organ shortage was less pronounced), which could result in an artificial mortality decrease. That is, decreased mortality rates would be due to improvements in the HD casemix not captured by existing covariables, rather than improvements in HD methods. Based on the PD trends study, it could be concluded that the decreasing trend in mortality was not an artifact due to "competing" causes of transfer from PD. In the current investigation, we are less certain that corresponding trends in transplant rates do not contribute to the decrease.

Supplementary analysis revealed that the calendar period in which HD was received was a stronger predictor of mortality than the period of HD-initiation. That is, the improvement in mortality appears to occur crosssectionally over calendar time, as opposed to longitudinally within patient cohorts. This is consistent with the hypothesis that improvements in HD are applied by clinicians to patients cross-sectionally, rather than within cohorts. If, despite therapeutic enhancements, patients received HD uniformly and in the same manner as when they initiated HD, then the "cohort" effect would have appeared stronger than the "period" effect. Since this is apparently not the case, in classifying patients by cohort, we are comparing heterogeneous mixtures of HD.

Inference based on our results is most impaired by the dearth of published information on HD practice patterns. In Canada, little quantitation of even the current state of HD is available, let alone data on changes therein over time. This makes it impossible to determine the extent to which each of the methodological changes in HD is responsible for the decrease in mortality rates. Future studies should attempt to accurately document HD practice patterns in order that changes therein may be quantitated and correlated with corresponding changes in patient outcomes.

We observed a significant decrease in adjusted hemodialysis mortality rates in Canada during the 1981–1987 period. The mortality decline is primarily related to the several improvements in HD methods and practices which occurred during that period. Since the observed decreasing mortality trend did not appear to level off, and since further improvement in dialysis equipment and technology are possible and even predicted [26, 27], continued reductions in HD mortality can likely be expected.

ACKNOWLEDGMENTS

This investigation was funded by Baxter Healthcare Corporation, Renal Division, Deerfield, IL. The collection of data and the maintenance of the Canadian Organ Replacement Register is made possible by the wholehearted collaboration of the 86 individual renal programs across Canada. The contribution of the current and past full-time staff assigned to the Register at the Canadian Institute for Health Information (formerly, Hospital Medical Records Institute) also has been essential to the success of the Register. The Canadian Society of Nephrology, The Canadian Transplant Society, The Canadian Association of Transplantation, and the Canadian Association of Nephrology, nurses and technicians and their constituent members also have made an essential contribution to the Register since its inception in 1981. CORR is funded 15% by the federal department of health, and 80% by the provincial and territorial departments of health based on population. Together, the Kidney Foundation of Canada and the health care industry provide approximately 5% of the funding.

Reprint requests to Dr. Stanley S.A. Fenton, The Toronto General Hospital, 200 Elizabeth Street, 13th Floor, Eaton Wing North, Room 232, Toronto, Ontario M5G 2C4, Canada. E-mail: stanley.fenton@uhn.on.ca

REFERENCES

- 1. SCRIBNER BH, BURI R, CANER JEZ, HEGSTROM R, BURNELL JM: The treatment of chronic uremia by means of intermittent dialysis: a preliminary report. *Trans Am Soc Artif Organs* 6:114–119, 1960
- 2. PASTAN S, BAILEY J: Dialysis therapy. N Engl J Med 338:1428–1437, 1998
- HAKIM RM, BREYER J, ISMAIL N, SCHULMAN G: Effects of dose of dialysis on morbidity and mortality. *Am J Kidney Dis* 23:661–669, 1994
- PARKER T, HUSNI L, HUANG W, LEW N, LOWRIE EG, DALLAS NEPHROLOGY ASSOCIATES: Survival of hemodialysis patients in the Unites States is improved with greater quantity of dialysis. *Am J Kidney Dis* 23:670–680, 1994
- HELD PJ, PORT FK, WOLFE RA, STANNARD DC, CARROLL CE, DAUGIRDAS JT, BLOEMBERGEN WE, GREER JW, HAKIM RM: The dose of hemodialysis and patient mortality. *Kidney Int* 50:550–556, 1996
- BLOEMBERGEN WE, STANNARD DC, PORT FK, WOLFE RA, PUGH JA, JONES CA, GREER JW, GOLPER TA, HELD PJ: Relationship of dose of hemodialysis and cause-specific mortality. *Kidney Int* 50:557–565, 1996
- HAKIM RM, WINGARD RL, PARKER RA: Effect of the dialysis membrane in the treatment of patients with acute renal failure. N Engl J Med 331:1338–1342, 1994
- HAKIM RM, HELD PJ, STANNARD DC, WOLFE RA, PORT FK, DAU-GIRDAS JT, AGODOA L: Effect of the dialysis membrane on mortality of chronic hemodialysis patients. *Kidney Int* 50:566–570, 1996
- LAZARUS JM, OWEN WF: Role of bioincompatibility in dialysis morbidity and mortality. Am J Kidney Dis 24:1019–1032, 1994
- HAKIM RM: Influence of the dialysis membrane on outcome of ESRD patients. Am J Kidney Dis 32(Suppl. 4):S71–S75, 1998
- ESCHBACH JW, EGRIE JC, DOWNING MR, BROWNE JK, ADAMSON JW: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. N Engl J Med 316:73–78, 1987
- 12. CANADIAN ERYTHROPOIETIN STUDY GROUP: Association between recombinant human erythropoietin and quality of life and exercise

capacity of patients receiving haemodialysis. Br Med J 300:573-578, 1990

- DIAMOND SM, HENRICH WL: Acetate dialysate versus bicarbonate dialysate: a continued controversy. Am J Kidney Dis 9:3–11, 1987
- WOLFE RA, PORT FK, HAWTHORNE VM, GUIRE KE: A comparison of survival among dialytic therapies of choice: In-center hemodialysis versus continuous ambulatory peritoneal dialysis at home. Am J Kidney Dis 15:433–440, 1990
- NELSON CB, PORT FK, WOLFE RA, GUIRE KE: Comparison of continuous ambulatory peritoneal dialysis and hemodialysis patient survival with evaluation of trends during the 1980s. J Am Soc Nephrol 3:1147–1155, 1992
- WOLFE RA, HELD PJ, HULBERT-SHEARON TE, AGODOA LYC, PORT FK: A critical examination of trends in outcomes over the last decade. Am J Kidney Dis 32(Suppl. 4):S9–S15, 1998
- PORT FK, ORZOL SM, HELD PJ, WOLFE RA: Trends in treatment and survival for hemodialysis patients in the United States. Am J Kidney Dis 32(Suppl. 4):S34–S38, 1998
- CANADIAN ORGAN REPLACEMENT REGISTER: Annual Report 1998: Dialysis and Renal Transplantation, Ottawa, Canadian Institute for Health Information, 1998

- BERRY G: The analysis of mortality by the subject-years method. Biometrics 39:173–180, 1983
- FROME EL: The analysis of rates using Poisson regression models. Biometrics 39:665–674, 1983
- HEMODIALYSIS ADEQUACY WORKING GROUP: NKF-DOQI clinical practice guidelines for hemodialysis. *Am J Kidney Dis* 30(Suppl. 2):S15–S66, 1997
- 22. US RENAL DATA SYSTEM: USRDS 1998 Annual Data Report. Bethesda, MD, National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases, 1998
- HULL AR: The 1989 morbidity and mortality meeting: How far have we come? Am J Kidney Dis 32(Suppl. 4):S6–S8, 1998
- Proceedings from the Morbidity Mortality, Prescription of Dialysis Symposium, Dallas, Texas. Am J Kidney Dis 15:375–511, 1990
- 25. SCHAUBEL DE, FENTON SSA: Trends in mortality on peritoneal dialysis: Canada: 1981–97. J Am Soc Nephrol, in press
- HENDERSON LW: Dialysis in the 21st century. Am J Kidney Dis 6:951–957, 1996
- 27. CHEUNG AK: Stages of future technological developments in haemodialysis. *Nephrol Dial Transplant* 11(Suppl. 8):52–58, 1996