Intensive Hemodialysis Associates with Improved Survival Compared with Conventional Hemodialysis

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ABSTRACT

Patients undergoing conventional maintenance hemodialysis typically receive three sessions per week, each lasting 2.5–5.5 hours. Recently, the use of more intensive hemodialysis (>5.5 hours, three to seven times per week) has increased, but the effects of these regimens on survival are uncertain. We conducted a retrospective cohort study to examine whether intensive hemodialysis associates with better survival than conventional hemodialysis. We identified 420 patients in the International Quotidian Dialysis Registry who received intensive home hemodialysis in France, the United States, and Canada between January 2000 and August 2010. We matched 338 of these patients to 1388 patients in the Dialysis Outcomes and Practice Patterns Study who received in-center conventional hemodialysis during the same time period by country, ESRD duration, and propensity score. The intensive hemodialysis group received a mean (SD) 4.8 (1.1) sessions per week with a mean treatment time of 7.4 (0.87) hours per session; the conventional group received three sessions per week with a mean treatment time of 3.9 (0.32) hours per session. During 3008 patient-years of follow-up, 45 (13%) of 338 patients receiving intensive hemodialysis died compared with 293 (21%) of 1388 patients receiving conventional hemodialysis (6.1 versus 10.5 deaths per 100 person-years; hazard ratio, 0.55 [95% confidence interval, 0.34–0.87]). The strength and direction of the observed association between intensive hemodialysis and improved survival were consistent across all prespecified subgroups and sensitivity analyses. In conclusion, there is a strong association between intensive home hemodialysis and improved survival, but whether this relationship is causal remains unknown.

J Am Soc Nephrol 23: 696–705, 2012. doi: 10.1681/ASN.2011070676

Received July 11, 2011. Accepted December 19, 2011.

Published online ahead of print. Publication date available at www.jasn.org.

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ESRD is a prevalent condition with impaired quality of life and survival. Given the scarcity of transplantable donor kidneys, hemodialysis remains the dominant form of renal replacement therapy in the developed world. Complications of uremia, associated comorbidities, and the hemodialysis treatment itself likely contribute to the excess mortality associated with ESRD.[1,2]

Lengthening dialysis session times to >5.5 hours provides substantially greater solute clearance and extracellular fluid volume control, potentially leading to improved outcomes.[3–5] Unfortunately, there are no randomized trials evaluating the effects of extended hours hemodialysis regimens on survival. Previous observational studies have suggested that lengthening hemodialysis session time to >6 hours, and increasing frequency to ≥5 treatments per week may be associated with improved survival.[6,7] However, these studies only examined frequent extended hours hemodialysis. Moreover, they were limited by use of nonideal control groups,[6] potential immortal time bias,[8] and informative censoring for switches back to conventional hemodialysis.[6] To improve upon the results of previous studies, we undertook this multinational cohort study. Our goals were to evaluate the hypothesis that intensive hemodialysis is associated with improved survival over conventional hemodialysis, and to obtain a more valid estimate of the magnitude of this association.

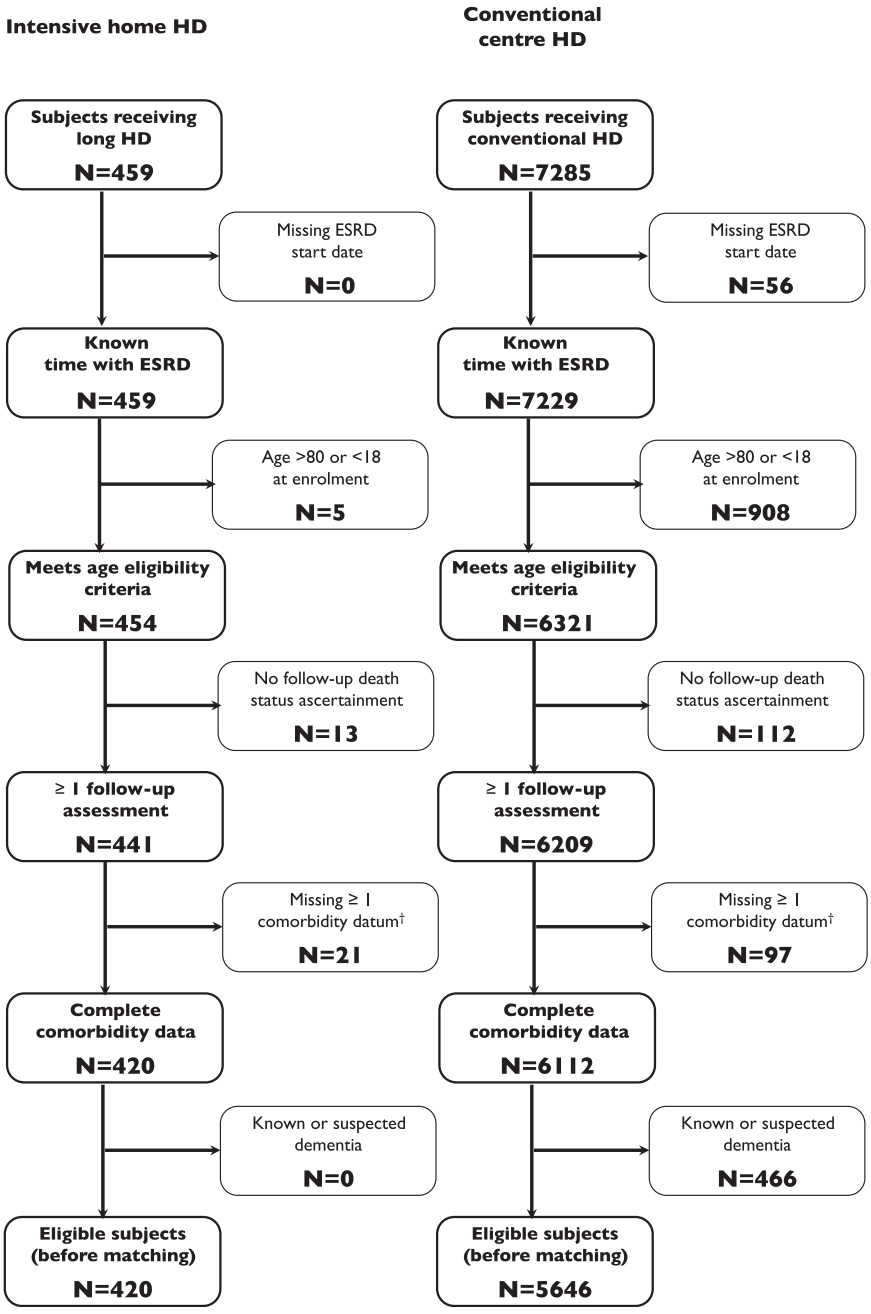

Figure 1. Study cohort assembly showing eligible patients and exclusions. Because there were no patients with dementia receiving intensive dialysis, patients with dementia were excluded from the conventional dialysis group. HD, hemodialysis. †Patients missing data for any of the following comorbid conditions were excluded: diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, or cancer (hematologic and solid organ malignancies combined into a single aggregate variable).

RESULTS

Study Sample, Baseline Characteristics, and Dialysis Prescriptions

There were 6066 patients (420 intensive, 5646 conventional) who met eligibility criteria (Figure 1). After matching, there were 338 intensive hemodialysis patients and 1388 conventional hemodialysis patients available for analysis. There were small residual between-group differences in age, sex, vascular access, and prevalence of chronic obstructive lung disease (Table 1). Laboratory variables and BPs remained significantly different between groups even after matching, as these were taken ≥6 weeks after starting intensive hemodialysis in that group (Table 2).

We newly started 172 (51%) patients on intensive hemodialysis during the study observation period, whereas 49% had already started intensive hemodialysis before study enrollment. Treatment time averaged 7.4±0.87 hours for intensive hemodialysis patients, compared with 3.9±0.32 hours for conventional patients (Table 1). The intensive hemodialysis group received a mean treatment frequency of

Table 1. Patient characteristics at cohort entry, before and after matching

Variable	Before Matching (Overall Sample)			After Matching		
	Intensive Hemodialysis (*n*=420)	Conventional Hemodialysis (*n*=5643)	Standardized Difference (%)	Intensive Hemodialysis (*n*=338)	Conventional Hemodialysis (*n*=1388)	Standardized Difference (%)
Demographic, %						
age (yr), mean (SD)	49.6 (12.3)	59.3 (13.8)	74.4	50.8 (12.4)	52.3 (12.4)	11.3
18–29	6.2	3.3	13.4	5.6	7.7	8.3
30–39	16.9	6.4	33.0	15.4	12.4	8.6
40–49	27.1	13.3	34.9	24.3	21.9	5.6
50–59	29.3	22.2	16.3	31.1	24.0	16.0
60–69	16.2	26.9	26.2	18.6	20.1	3.7
70–79	4.3	27.8	67.7	5.0	13.6	29.8
male sex	71.7	55.0	35.2	70.4	64.2	13.3
race						
white	77.4	65.2	27.2	75.4	72.5	6.7
black	6.4	24.1	50.7	7.4	11.5	14.2
other	16.2	10.7	16.2	17.2	16.0	3.2
country						
Canada	73.3	17.1	137.0	71.0	71.0	0.0
France	14.8	18.3	9.5	14.5	14.5	0.0
United States	11.9	64.6	129.1	14.5	14.5	0.0
Duration of ESRD (mo), mean (SD)	7.3 (7.6)	3.3 (4.7)	63.3	5.7 (6.2)	5.7 (3.1)	0.0
0–6	6.9	26.9	55.4	8.6	9.8	4.1
6–12	6.7	11.4	16.4	8.3	8.0	1.1
12–18	6.4	8.4	7.4	6.8	5.9	3.6
18–24	8.3	7.0	5.2	9.8	8.6	4.1
24–36	5.7	6.2	2.0	6.5	7.4	3.5
36–42	5.0	5.2	0.8	5.6	4.7	4.0
42–48	3.8	4.6	4.1	4.1	4.4	1.5
48–54	2.6	3.9	7.4	3.0	4.7	9.2
>54	54.5	26.5	59.7	47.3	46.2	2.4
Dialysis prescription, %						
dialysis sessions per week, mean (SD)	4.8 (1.1)	3.0 (0)	231.4	4.8 (1.1)	3.0 (0)	231.4
minutes per dialysis session, mean (SD)	441 (52)	226 (30)	506.5	441 (52)	236 (13)	540.9
vascular access type[a]						
fistula	56.0	43.2	25.6	53.3	55.9	5.3
catheter	21.7	31.5	22.4	24.6	25.1	1.4
graft	5.5	21.0	47.1	5.3	15.1	32.7
other or unknown	16.9	4.3	42.0	16.9	4.1	42.4
Comorbidities, %						
diabetes mellitus	24.0	50.3	56.4	28.1	27.2	2.0
myocardial infarction	11.4	19.4	22.2	13.0	13.0	0.0
congestive heart failure	13.1	32.0	46.4	13.9	15.1	3.4
peripheral vascular disease	10.7	31.7	53.1	12.4	14.8	6.9
cerebrovascular disease	5.0	15.6	35.4	5.9	5.9	0.0
chronic obstructive pulmonary disease	7.6	13.4	19.0	6.8	9.5	9.8
cancer	11.2	12.6	4.4	11.2	12.7	4.6

[a]Missing vascular access type in 11% and 5% in intensive and conventional groups, respectively.

Table 2. Predialysis laboratory and BP values

Variable	Before Matching (Overall Sample)			After Matching		
	Intensive Hemodialysis (*n*=420)	Conventional Hemodialysis (*n*=5643)	Standardized Difference (%)	Intensive Hemodialysis (*n*=338)	Conventional Hemodialysis (*n*=1388)	Standardized Difference (%)
Laboratory measures, mean (SD)						
serum albumin (g/dl)[a]	3.9 (0.5)	3.7 (0.5)	40.0	3.8 (0.5)	3.7 (0.4)	36.7
hemoglobin (g/dl)[b]	11.8 (1.5)	11.5 (1.5)	17.3	11.8 (1.5)	11.5 (1.2)	18.2
phosphorous (mg/L)[a]	4.4 (1.6)	5.6 (1.9)	67.7	4.3 (1.5)	5.6 (1.5)	80.0
calcium (mg/L)[c]	9.2 (0.9)	9.2 (0.8)	0.0	9.2 (0.8)	8.8 (0.6)	63.7
urea (mg/L)[a]	40 (20)	60 (20)	109.8	39 (20)	62 (16)	130.2
BP, mean (SD)						
systolic BP (mmHg)[a]	131 (21)	148 (26)	71.9	130 (21)	146 (16)	138.0
diastolic BP (mmHg)[a]	74 (13)	78 (16)	27.4	74 (13)	81 (10)	62.4

For intensive patients, these measures were taken at least 6 weeks after starting intensive dialysis. For conventional patients, they were taken at the time of patient entry into the database. Linear regression was used to compare differences in laboratory values and BP between intensive and conventional matched groups.
[a] $P<0.001$.
[b] $P=0.03$.
[c] $P=0.41$.

4.8±1.1 sessions per week, with 119 (35%) patients receiving three to four sessions per week and 219 (65%) receiving five to seven sessions per week.

Follow-Up and Competing Events

The total follow-up time was 3008 patient-years (median follow-up, 1.8 years; 25th percentile, 0.8 years; 75th percentile, 2.6 years; maximum truncated at 4.0 years). Seventy intensive hemodialysis patients and 146 conventional patients received renal transplants. The transplant rates per 100 person-years were 9.5 (95% confidence interval [95% CI], 7.6–12.1) and 8.8 (95% CI, 6.7–11.6), respectively. No patient receiving conventional dialysis switched dialysis modality, whereas 48 intensive dialysis patients switched to conventional in-center hemodialysis. Nineteen patients on intensive hemodialysis relocated to a new dialysis facility, but were confirmed alive 90 days after transfer. No patients on conventional hemodialysis relocated.

Patient Survival

Survival analyses are summarized in Table 3. The results showed that 45 of the 338 patients receiving intensive hemodialysis died (6.1 deaths per 100 person-years; 95% CI, 4.6–8.2), whereas 293 of 1388 patients receiving conventional hemodialysis died (10.5 deaths per 100 person-years; 95% CI, 8.1–13.5). Compared with in-center conventional hemodialysis, the hazard ratio (HR) for death associated with intensive hemodialysis was 0.55 (95% CI, 0.34–0.87; $P=0.01$) (Figure 2). Adjusting for age, sex, race, and diabetes yielded identical results.

All sensitivity analyses (Table 3) yielded similar HRs as for the primary analysis. Two analyses limiting the intensive hemodialysis cohort to new users ($n=172$) and patients dialyzed three times per week ($n=61$) resulted in similar point estimates but wider confidence intervals that spanned a HR of 1.0. Results of the subgroup analyses are provided in Figure 3. To note, the HR for death in intensive hemodialysis patients receiving three to four sessions per week compared with conventional hemodialysis was 0.34 (95% CI, 0.13–0.92; $P=0.03$).

DISCUSSION

Intensive hemodialysis has been in use for decades.[9] The greater removal of fluid and uremic waste afforded by this regimen are in turn associated with improved BP,[10] endothelial function,[11] and ventricular mass,[12] all of which are important predictors of survival in persons with ESRD. However, given the potentially greater burden associated with more intensive therapy, well designed studies evaluating hard endpoints are needed.

This study demonstrates a strong association between intensive home hemodialysis and patient survival. Previous reports have also suggested survival benefits with intensive hemodialysis. In a study of prevalent Canadian patients, Pauly *et al.* reported a 5-year survival rate of 85% among patients receiving home intensive hemodialysis, a rate comparable with that of patients who had received a deceased donor transplant in the United States.[6] In that study, patients switching back to conventional hemodialysis were censored without subsequent follow-up. This can result in informative censoring, whereby imminent deaths on intensive hemodialysis are not counted. Johansen *et al.* compared home intensive with in-center conventional dialysis, using propensity score matching, and reported a HR of 0.36 (95% CI, 0.22–0.61) for death, favoring intensive hemodialysis.[7] However, this study did not account for immortal time bias or differences in time with ESRD (vintage) before study enrollment. We obtained more conservative treatment effect estimates (4-year survival, 75%; HR for death, 0.55) after eliminating immortal time bias and informative censoring.

Table 3. HRs for all-cause mortality in primary and sensitivity analyses

Group	Number of Patients	Number of Events	Deaths per 100 Person-Years	HR (95% CI)
Primary analysis				
matched sample, no censoring for modality switches				
conventional HD (referent)	1388	287	11	1
intensive HD	338	45	6	0.55 (0.34–0.87)
matched sample, no censoring for modality switches (adjusted)[a]				
conventional HD (referent)	1388	287	11	1
intensive HD	338	45	6	0.53 (0.33–0.86)
Sensitivity analyses				
matched sample, with censoring for modality switches				
conventional HD (referent)	1388	287	11	1
intensive HD	338	38	6	0.51 (0.31–0.84)
unmatched sample, no censoring for modality switches				
conventional HD (referent)	5646	1301	15	1
intensive HD	420	54	6	0.39 (0.29–0.52)
matched sets with 2:1 matching (conventional/intensive HD)				
conventional HD (referent)	563	98	10	1
intensive HD	338	45	6	0.60 (0.37–0.97)
matched sets receiving 3 dialysis sessions per week				
conventional HD (referent)	298	43	9	1
intensive HD	61	7	5	0.40 (0.11–1.52)
worst-case scenario for missing vascular access data[b]				
conventional HD (referent)	1388	287	11	1
intensive HD	338	45	6	0.56 (0.34– 0.91)
matched sets with additional matching by year (era) of study enrollment				
conventional HD (referent)	893	199	14	1
intensive HD	221	38	7	0.61 (0.41–0.91)
matched sets with new intensive hemodialysis users				
conventional HD (referent)	681	129	10	1
intensive HD	172	28	7	0.66 (0.36–1.24)
matched sets with exclusion of secondary data sources				
FMCNA excluded				
conventional HD (referent)	1073	221	10	1
intensive HD	304	43	6	0.59 (0.36–0.97)
REIN excluded				
conventional HD (referent)	1159	260	11	1
intensive HD	289	39	7	0.56 (0.34–0.92)
BCRA excluded				
conventional HD (referent)	1030	206	10	1
intensive HD	227	24	5	0.43 (0.23–0.81)
unmatched cohorts, no censoring for modality switches[c]				
conventional HD (referent)	5646	1301	15	1
intensive HD	420	54	6	0.66 (0.49–0.89)

All analyses unadjusted unless otherwise specified.
[a]Adjusted for variables not achieving <10% standardized difference after matching. Final model included the following covariates: age at index, sex, race, and diabetes.
[b]Worst-case scenario was defined as follows: all missing access type in intensive hemodialysis cohort imputed as fistula; missing access in conventional hemodialysis group imputed as catheters.
[c]Final model included the following covariates: age at index, sex, race, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, and cancer.

Our study has several additional strengths. Patients receiving intensive hemodialysis in this study were likely a select group. Propensity score matching allowed us to reduce the effect of selection bias by drawing similarly selected individuals from a large pool of conventional hemodialysis recipients. Despite large between-group differences in the unmatched sample, our matching strategy resulted in a virtually identical distribution of observed covariates, and >80% of intensive hemodialysis patients matched. Furthermore, similar rates of transplantation in the matched cohorts suggest that

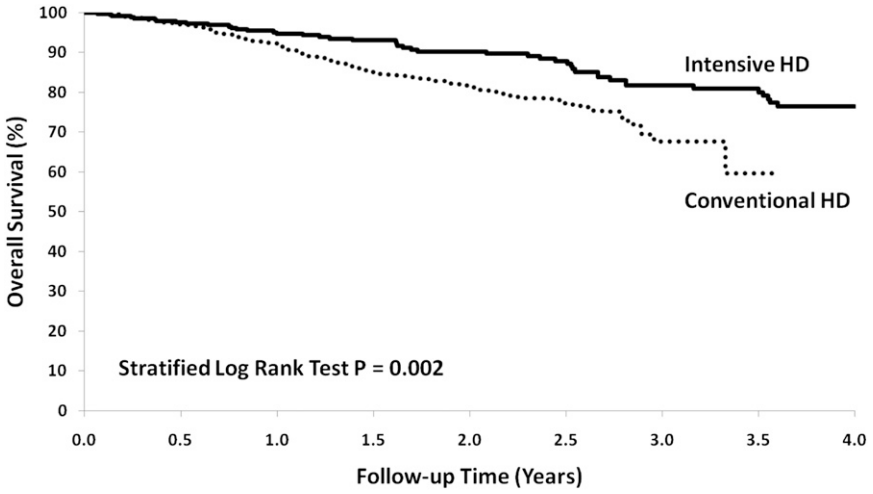

Figure 2. Kaplan–Meier plot for intensive and conventional hemodialysis. Two-sided *P*=0.002 by log-rank test, stratified by matched set and country. HD, hemodialysis.

Subgroup	No. of Patients IHD	No. of Patients CHD	Event Rate per 100 Person-Years IHD	Event Rate per 100 Person-Years CHD	Hazard Ratio (adjusted)	Interaction P-value
Overall	338	1388	6.1	12.6	0.538	
Age						
< 52 yr *	169	601	3.6	10.8	0.363	0.36
≥ 52 yr	169	787	8.6	14.0	0.604	
Country						
Canada	240	702	6.7	13.6	0.615	Referent
France	49	229	4.5	7.2	0.438	0.69
US	49	457	5.5	13.9	0.226	0.17
Cardiac History						
MI or CHF	72	436	9.4	17.7	0.488	0.97
No MI, no CHF	266	952	5.2	10.3	0.500	
Duration of ESRD						
< 1.0 yr	57	300	5.8	9.2	0.647	Referent
1.0 yr to 3.5 yr **	111	439	9.0	12.2	0.954	0.65
≥ 3.5 yr	170	649	4.7	14.1	0.316	0.39
Frequency per week						
< 5 times	119	648	3.8	10.9	0.342	0.30
≥ 5 times	219	740	7.5	14.1	0.623	

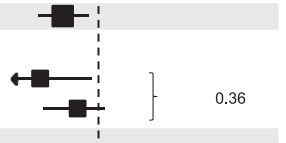

Figure 3. Subgroup analyses for matched cohorts (unadjusted). *P* values for interactions are based on *z* tests. IHD, intensive hemodialysis; CHD, conventional hemodialysis; MI, myocardial infarction; CHF, congestive heart failure. *Median age at cohort entry is 52 years. **Median duration of ESRD at cohort entry is 3.5 years.

unobserved prognostic variables were likely balanced as well. A number of additional methodological features strengthen the validity of our findings. Because mortality in ESRD can vary widely by country, we included country of residence in our matching strategy.[13] We also matched patients closely by duration of ESRD to eliminate immortal time bias.[8] This design element also eliminated survivor bias that occurs when prevalent cross-sections of patients are included rather than new incident patients. To note, restricting our analysis to new users did not alter the effect estimate (HR, 0.66; 95% CI, 0.36–1.24). Rather than censor patients upon switching to conventional hemodialysis,[6] we followed patients for outcomes for at least 90 days after they switched back to conventional hemodialysis, eliminating the potential for informative censoring. Finally, we included patients from various countries with different demographic composition, which increases the generalizability of our findings.

It is well recognized that an observational study design can demonstrate association only, and not causality. Therefore, despite the use of propensity score matching, we cannot exclude residual confounding as a potential explanation for our results. It is plausible that the intensive hemodialysis group members had better survival because they are a select, more motivated group, and that our propensity score models did not capture these characteristics. Although we do not have any information on functional status or motivation, the fact that the transplant rates were similar in both groups is reassuring that the groups were unlikely to differ with respect to these factors. Furthermore, after adjusting for similar variables as used in our study, Woods *et al.* did not observe any further difference in survival after adjusting for mobility, income, and education in a comparison of home versus center hemodialysis.[14] It is also noteworthy that recent comparisons of home peritoneal dialysis and in-center hemodialysis show similar survival of these modalities.[15] Thus, although a "home versus center" effect likely exists, it is unlikely to account for all of the survival benefits associated with intensive hemodialysis in this study. The strength of the observed association as well as consistency in the HRs across all prespecified subgroups further supports this assertion. Finally, that we observed large differences in BP and laboratory values after the initiation of intensive hemodialysis is consistent with a previous clinical trial.[12] These changes are therefore likely causally linked to intensive hemodialysis, and summarily provide a plausible biologic mechanism by which more intensive hemodialysis may improve survival.

Our study has some limitations. We were unable to match on vascular access type due to missing data, and dialysis with a

fistula is associated with better outcomes. However, our sensitivity analysis whereby we assumed all intensive patients with missing access data had a fistula, and all conventional patients with missing data had a catheter, yielded a similar HR to the primary analysis. Our study sample included patients drawn from a number of databases; hence, information bias may have been present. However, the exclusion of each source of secondary data from the study sample did not change the effect estimate. We did not have any data on adherence to the dialysis prescription or medication use. However, in the recently completed Frequent Hemodialysis Network nocturnal trial, patients undergoing frequent home nocturnal hemodialysis were more likely to miss sessions than patients undergoing conventional hemodialysis.[16] This would have been more likely to attenuate any survival benefits associated with intensive hemodialysis in our study. Finally, as mentioned, we were unable to account for potential home versus center effects. Residual confounding is best addressed by randomized trials. Unfortunately, large trials of intensive dialysis with adequate statistical power to examine mortality have not yet been feasible[17] nor have prospective observational studies comparing home conventional to home intensive dialysis. Thus, notwithstanding its limitations, our study represents the most rigorously conducted observational study in this field to date.

In summary, we found that intensive home hemodialysis is associated with markedly improved patient survival compared with conventional in-center hemodialysis. In this observational study, we cannot disentangle the relative effects of the home environment, unmeasured patient characteristics, or the model of care from the effects of dialysis prescription itself. On the other hand, we cannot exclude the possibility that increasing dialysis frequency and duration may improve survival. There are additional factors that make intensive hemodialysis appealing to many patients. These include liberalization of the diet (fluid, phosphorous, protein, potassium), flexible scheduling, and free daytime hours in the case of nocturnal therapy. Finally, intensive hemodialysis, when performed at home, can be provided at a lower cost than center hemodialysis.[18] For all of these reasons, we believe that intensive home hemodialysis should be considered by patients, providers, and physicians when discussing the many treatment options for ESRD.

CONCISE METHODS

Study Design and Setting

We obtained data from two multinational renal databases on patients receiving intensive and conventional hemodialysis: the International Quotidian Dialysis Registry (IQDR), and the Dialysis Outcomes and Practice Patterns Study (DOPPS), respectively. To optimize baseline prognostic balance between groups, we matched patients by country, duration of ESRD before study enrollment, and propensity score. All analyses adhered to a detailed, predefined study protocol and followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Supplemental Material).[19]

Data Sources

Detailed methods for IQDR and DOPPS were previously described.[20,21] In brief, the IQDR captures detailed demographic, clinical, dialysis prescription, and outcomes data on incident and prevalent patients receiving more frequent ($\geq$5 sessions per week) or long ($>$5.5 hours per session) hemodialysis. None of the patients received hemodialysis with the NxStage device. Participation in the IQDR is voluntary, and data are collected in two ways. Primary IQDR data were prospectively abstracted from medical charts and entered into web-based electronic case report forms by trained research personnel. Demographics and comorbidities were entered at the time that patients were registered in the database. Prescription data, dialysis modality changes, and transplantation and vital status were updated semiannually. All centers confirmed vital status in August 2010. All patients provided written consent.

Secondary IQDR data were obtained through direct electronic transfer from the Renal Epidemiology and Information Network (REIN),[22] Fresenius Medical Care North America (FMCNA), and Patient Records and Outcome Management Information System (PROMIS) databases. REIN and PROMIS prospectively capture detailed data for all patients receiving dialysis in France and British Columbia, Canada, respectively, whereas FMCNA does the same for patients receiving hemodialysis in facilities run by Fresenius in the United States. Comorbidities were entered when patients began renal replacement therapy, whereas prescription, vital status, and modality changes were updated as they occurred. De-identified extracts on patients receiving frequent or long hemodialysis in these databases were prepared according to variable coding used by the IQDR.

The DOPPS prospectively captures detailed patient- and facility-level data on randomly selected participants from randomly selected hemodialysis units in 13 participating countries.[20] All patients provided written consent. Trained research personnel abstracted demographic, clinical, and dialysis prescription data from medical charts at the time of patient entry into DOPPS. Vital status, transplantation, and dialysis modality switches were updated every 4 months.

Data collection periods were as follows: January 1, 2000 to August 4, 2010 (primary IQDR data); January 1, 2002 to December 31, 2008 (REIN); June 1, 2002 to August 14, 2010 (PROMIS); January 1, 2007 to March 4, 2009 (FMCNA); and January 1, 2002 to December 31, 2008 (DOPPS).

Study Sample

All participants were aged $\geq$18 years at enrollment. We included patients receiving intensive hemodialysis, defined as $\geq$5.5 hours per session (day or overnight), three to seven sessions per week. Intensive hemodialysis was performed at home. For the comparator group, we selected patients receiving conventional hemodialysis for $<$5.5 hours per session, three sessions per week, in a clinic or hospital setting.

Study Variables

Patients already receiving intensive hemodialysis at enrollment had a period of guaranteed survival, or "immortal" time, spanning the intensive hemodialysis start date and study enrollment date. The index date was thus defined as the date of enrollment to prevent immortal time bias, which would have arisen had we used the start of intensive

hemodialysis as the index date. We calculated the duration of ESRD before study enrollment as the index date minus the first ESRD treatment date. Comorbidities coded with the *International Classification of Diseases, Ninth Edition* classification (FMCNA data) were re-classified into Charlson Comorbidity Index definitions for standardization purposes, but were treated as individual covariates in statistical models.[23]

Matching Procedures

We selected patients from the above-defined cohorts using propensity score matching to account for systematic differences between conventional and intensive hemodialysis patients. The propensity score is the probability of receiving intensive hemodialysis, conditional on the observed baseline covariates.[24] Conventional and intensive hemodialysis patients with the same propensity score will have similar distributions of observed baseline covariates, reducing the effect of selection bias.

We estimated propensity scores with logistic regression, regressing type of hemodialysis (intensive versus conventional) using the following covariates: age, sex, diabetes, myocardial infarction, congestive heart failure, cerebrovascular disease, cancer, race, and dry weight.[25] Variables were chosen for the propensity score model on the basis of their associations with mortality or treatment selection.[25] Laboratory and BP variables were not included in the propensity score models because they were obtained after patients started intensive hemodialysis. We estimated the propensity score model separately for each country. We excluded patients receiving conventional hemodialysis with a propensity score <0.001 so that patients on conventional hemodialysis had a nonzero probability of receiving intensive hemodialysis. The distribution of propensity scores between groups is shown in the Supplemental Material.

We then matched patients by country, duration of ESRD (± 6 months), and propensity score, with up to 10 conventional hemodialysis patients for each intensive hemodialysis patient, using a "greedy-matching" (nearest-neighbor) algorithm.[24] We compared differences between matched conventional and intensive hemodialysis patients using standardized differences.[26] We evaluated various caliper widths iteratively until between-group standardized differences were minimized. The final selected propensity score caliper width was 0.06. Each conventional patient variable was weighted by the inverse of the number of conventional patients in that matched set when computing standardized differences.

Primary Survival Analyses

The primary outcome was all-cause mortality. For the primary analysis, we attributed all deaths to dialysis modality at index date, regardless of switches to other dialysis modalities. Patients were censored at transplantation in all analyses. We used the Kaplan–Meier product-limit method to calculate cumulative death rates and construct survival graphs for each group, and used the two-sided stratified log-rank test to compare differences between the curves.[27] We used Cox regression with and without multivariable adjustment to model survival. Models were stratified on the matched sets. The adjusted model included covariates that had standardized differences of $>10\%$ (Table 1).[28] We excluded laboratory values and BP from the multivariable models because they are influenced by intensive hemodialysis and were only available after the start of intensive hemodialysis. To test the proportional hazards assumption, we performed a global test of time-dependent covariates, which were created for all covariates in the model.[29] In models in which the proportional hazards assumption was not valid, we introduced time-dependent covariates to allow these covariates to have a time-varying effect. We used linear regression to compare laboratory and BP measurements between groups. We calculated 95% CIs for all HRs, and interpreted a two-tailed P value <0.05 as statistically significant. Missing data were not imputed. We used SAS 9.2 software (SAS Institute Inc, Cary, NC) for all analyses.

Sensitivity Analyses

We repeated the primary analysis with censoring of outcomes 90 days after a permanent modality switch; deaths within 90 days of a switch were attributed to the dialysis modality at index date. To reduce confounding that can occur with many-to-one matching, we repeated the primary analysis with 2:1 matching.[30] We then restricted the analysis to matched sets in which intensive hemodialysis patients received three treatments per week, and then separately analyzed matched sets in which intensive hemodialysis patients were newly started on intensive hemodialysis ("new users") at the time of cohort entry. To assess the effect of information bias arising from multiple secondary data sources, we repeated the primary analysis and excluded participants from each secondary data source (FMCNA, REIN, and PROMIS). To evaluate the potential effect of missing vascular access data, we conducted a worst-case scenario (maximum bias) sensitivity analysis, in which we repeated the primary survival comparison with the assumption that all patients with missing access type at baseline had fistulae in the intensive hemodialysis group and catheters in the conventional hemodialysis group. To examine for potential era effects, we repeated the primary analysis but this time also matched on year of index date. Finally, we constructed a multivariable Cox model that included all eligible patients (without matching). This model was stratified by country, and included covariates achieving $P<0.10$ using the two-variable screening method.

Subgroup Analyses

We repeated the primary analysis in the following five predefined subgroups: age, country, cardiovascular disease (a composite of myocardial infarction or congestive heart failure), duration of ESRD before index date, and dialysis frequency (3–4 versus ≥ 5 sessions per week). We used median values in the intensive hemodialysis group as the cut-point for continuous variables. For each subgroup, we re-matched patients based on the subgroup cut-off, while matching on propensity score, vintage, and country as in the primary analysis. We performed statistical tests for interaction to determine if the HRs for intensive hemodialysis and mortality differed significantly among subgroups.[31] To do so, we conducted a series of pair-wise comparisons using standard z tests.[32]

ACKNOWLEDGMENTS

We thank all centers who participated in the IQDR and DOPPS, and especially those individuals who entered data. We are also grateful

to the IQDR Scientific Committee and Advisory Board. Finally, we acknowledge Sarah Langford and the other research associates who assisted with coordination of the IQDR.

G.E.N. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. A.X.G. was funded by a clinician scientist award from the Canadian Institutes of Health Research. P.C.A. was supported by a career investigator award from the Heart and Stroke Foundation of Ontario. R.S.S. was supported by a randomized trials mentorship award from the Canadian Institutes of Health Research. This research was funded by unrestricted research grants from Baxter Healthcare Corporation, Gambro R&D, Fresenius Medical Care, and the Canadian Institutes for Health Research. R.M.L., A.X.G., and R.S.S. have an unrestricted research grant from Fresenius Medical Care Canada.

The funding bodies had no role in designing the study; in collecting, analyzing, or interpreting the data; or in preparing, reviewing, or approving this manuscript.

DISCLOSURES

None.

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This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2011070676/-/DCSupplemental.