Survival with Three-Times Weekly In-Center Nocturnal Versus Conventional Hemodialysis

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ABSTRACT

Whether the duration of hemodialysis treatments improves outcomes remains controversial. Here, we evaluated survival and clinical changes associated with converting from conventional hemodialysis (mean=3.75 h/treatment) to in-center nocturnal hemodialysis (mean=7.85 h/treatment). All 959 consecutive patients who initiated nocturnal hemodialysis for the first time in 77 Fresenius Medical Care facilities during 2006 and 2007 were eligible. We used Cox models to compare risk for mortality during 2 years of follow-up in a 1:3 propensity score–matched cohort of 746 nocturnal and 2062 control patients on conventional hemodialysis. Two-year mortality was 19% among nocturnal hemodialysis patients compared with 27% among conventional patients. Nocturnal hemodialysis associated with a 25% reduction in the risk for death after adjustment for age, body mass index, and dialysis vintage (hazard ratio=0.75, 95% confidence interval=0.61–0.91, P=0.004). With respect to clinical features, interdialytic weight gain, albumin, hemoglobin, dialysis dose, and calcium increased on nocturnal therapy, whereas postdialysis weight, predialysis systolic blood pressure, ultrafiltration rate, phosphorus, and white blood cell count declined (all $P<0.001$). In summary, notwithstanding the possibility of residual selection bias, conversion to treatment with nocturnal hemodialysis associates with favorable clinical features, laboratory biomarkers, and improved survival compared with propensity score–matched controls. The potential impact of extended treatment time on clinical outcomes while maintaining a three times per week hemodialysis schedule requires evaluation in future clinical trials.

J Am Soc Nephrol 23: 687–695, 2012. doi: 10.1681/ASN.2011070674

The contribution of dialysis time (*i.e.*, treatment duration) to outcomes in hemodialysis (HD) has been debated for several decades. Recently, the Hemodialysis Study failed to show a significant benefit of high dialysis doses three times per week,[1] prompting renewed interest in the role of modifying dialysis frequency and/or time beyond simply targeting a specific dose per treatment.[2] Although promising results were reported with short daily hemodialysis, concern was also raised regarding a potentially detrimental effect of more frequent cannulation on vascular access survival.[3] Other barriers to propagation of more frequent (more than three times per week) dialysis include patient preferences,[4] payment constraints (*e.g.*, payment for three treatments weekly or up to four with justification),[5] limited dialysis facility capacity, and availability of clinical personnel.[6] Thus, there is renewed interest in regimens that maintain a three times per week schedule but increase the overall treatment time per session.[7]

In the last few years, better laboratory and patient outcomes have been observed with three times per week in-center nocturnal hemodialysis (INHD) performed for more than 5.5 hours (generally about 8 hours) compared with three times per week conventional hemodialysis (CHD) performed for

Received July 11, 2011. Accepted November 4, 2011.

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

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3.0–5.5 hours.[8–16] The reports were mostly from single centers, with comparisons made between cohorts or using a crossover design within the same patients. As in all observational studies, selection bias, survival bias, and other limitations must temper interpretation of the findings. Nevertheless, these observational studies add to our fund of knowledge, filling in gaps when randomized clinical trials are not feasible or investigators are unable to obtain the necessary funding and support.

We previously reported better mortality and hospitalization outcomes associated with INHD compared with CHD patients.[15] While maintaining an observational cohort design in the current study, we addressed concerns about our prior report in two ways. (*1*) We modified patient inclusion criteria as solely based on initial (*i.e.*, first-ever) conversion from CHD to INHD. (*2*) We attenuated potential selection and treatment by indication biases by incorporating a propensity score–driven matching algorithm to define a suitable control group to evaluate comparative survival. We also used the controls to provide contextual secular trends in biomarkers over time.

RESULTS

The study cohort included 746 INHD patients matched by propensity score, geographic area, and incident patient status (vintage≤90 days versus vintage>90 days) to 2062 controls treated by CHD (Figure 1). Baseline patient characteristics (Table 1) revealed that patients on INHD were younger (52.8 versus 54.1 years, P=0.03) with shorter duration of ESRD (*i.e.*, less vintage; 2.9 versus 3.3 years, P=0.006) and slightly larger body mass index (*i.e.*, body mass index; 31.3 kg/m^2 versus 30.2 kg/m^2, P=0.02). The distribution of gender, race, diabetes, vascular access type, and laboratory biomarkers were similar between groups.

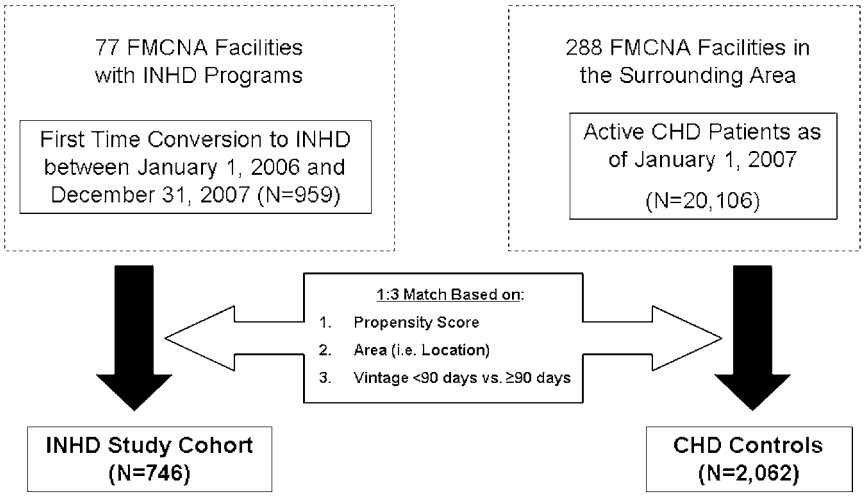

Figure 1. Enrollment algorithm. Patient flow into the study.

Table 1. Baseline patient characteristics

Characteristics at Baseline	In-Center Three Times per Week Chronic Hemodialysis		*P* Value
	Nocturnal	Conventional	
Patients (*N*)	746	2062	—
Age in years [mean (SD)]	52.8 (13.4)	54.1 (14.4)	0.03
Female (%)	32.3	34.2	0.40
Race (%)			0.60
black	51.0	48.8	—
white	46.3	48.1	—
other	2.7	3.1	—
Diabetes (%)	47.7	50.7	0.20
Vintage in years [mean (SD)]	2.9 (3.6)	3.3 (4.3)	0.006
Body mass index [kg/m^2; mean (SD)]	31.3 (8.8)	30.2 (8.8)	0.02
Vascular access (%)			0.70
fistula	37.0	35.4	—
graft	16.9	18.8	—
catheter	45.8	45.6	—
unknown	0.3	0.2	—
Laboratory values			
albumin [g/L; mean (SD)]	38 (4)	38 (4)	0.50
hemoglobin [g/dl; mean (SD)]	11.6 (1.4)	11.7 (1.2)	0.60
phosphorus [mmol/L; mean (SD)]	5.7 (1.6)	5.6 (1.6)	0.20
calcium [mmol/L; mean (SD)]	9.0 (0.8)	9.0 (0.8)	0.80
eKt/V [mean (SD)]	1.4 (0.3)	1.4 (0.3)	0.40
WBC count [×1000/mcl; mean (SD)]	7.4 (2.3)	7.3 (2.5)	0.90

WBC, white blood cell.

Patient Survival

One-year mortality rates were 9% for INHD and 15% for CHD controls, whereas 2-year mortality rates were 19% and 27%, respectively (30% absolute reduction). Two-year Kaplan–Meier survival curves (Figure 2) were better for INHD relative to CHD (log rank P<0.001), with a mortality hazard rate ratio (HR) of 0.67 [95% confidence interval=0.52–0.88, P=0.004] at 1 year and an HR of 0.69 (95% confidence interval=0.58–0.84, P<0.001) at 2 years (Figure 3). Second-stage Cox models that adjusted for residual differences in age, vintage, and body mass index indicated an HR of 0.73 (0.56–0.96, P=0.02) and an HR of 0.75 (0.61–0.91, P=0.004) at 1 and 2 years, respectively. Additional analyses censoring patients on switching modality had similar results (data not shown).

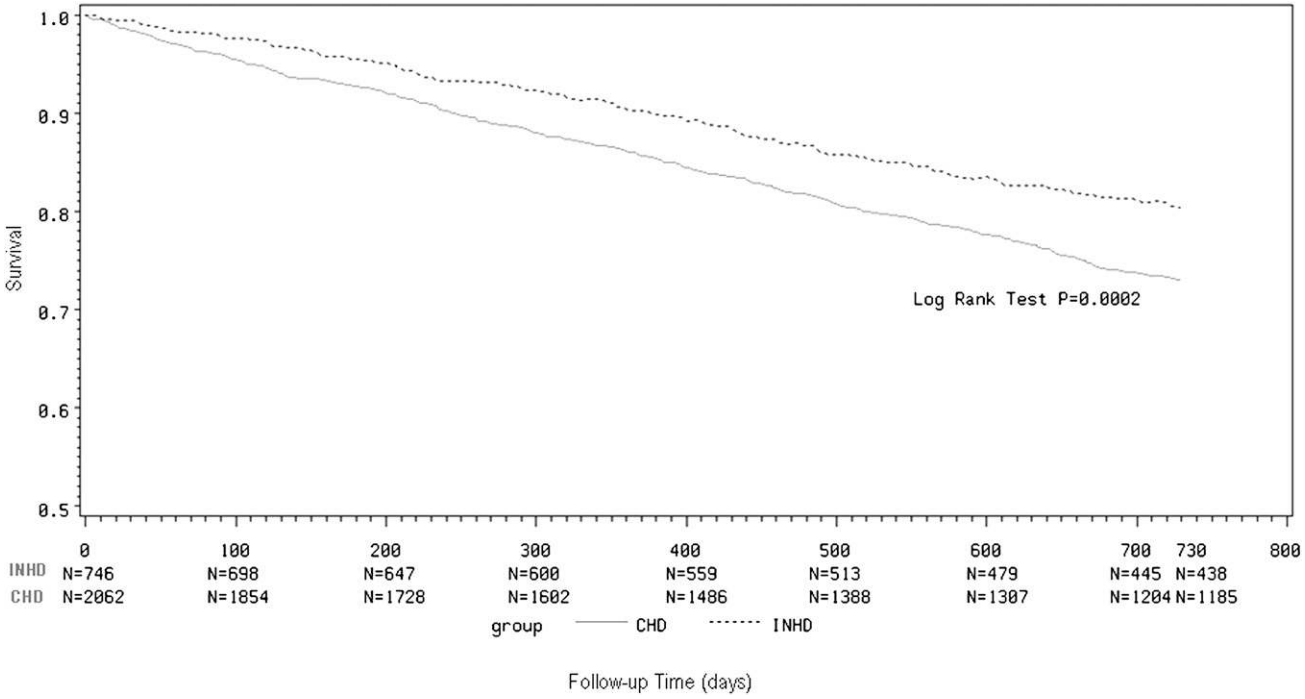

Figure 2. Enhanced INHD survival. Kaplan–Meier 2-year survival curves comparing patients on INHD (broken line) with patients on CHD (solid line).

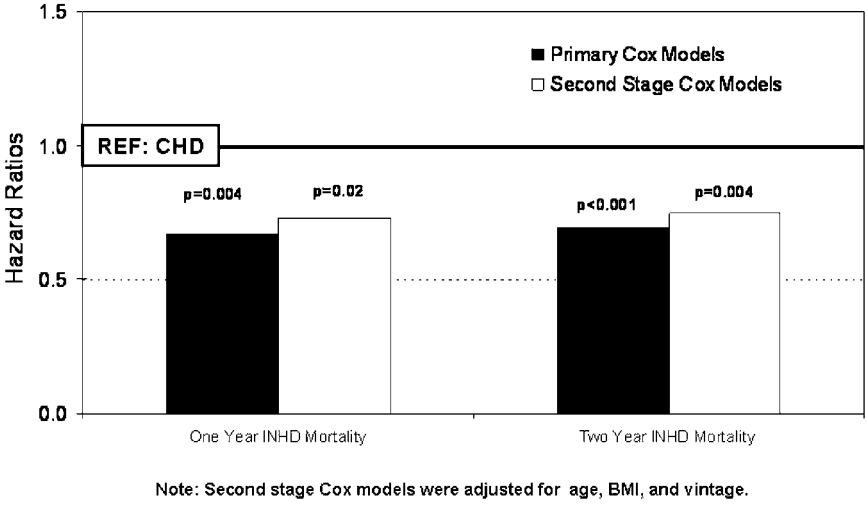

Figure 3. Enhanced adjusted INHD survival. Results from Cox proportional hazard models comparing time to death from patients treated by INHD with patients on CHD.

Changes Associated with Conversion to INHD

There were 725 patients (97%) who had at least one treatment on CHD before converting to INHD, with accompanying changes in dialysis prescription (Table 2). The conversion doubled dialysis time but was accompanied by prescription changes that lowered blood and dialysate flow rates as well as used smaller dialyzer surface area. Among these patients, 435 (60%) contributed data to all three distinct time periods: (*1*) 90-day baseline on CHD before conversion to INHD, (*2*) during the first 90 days of INHD, and (*3*) during the period from 91 to 180 days on INHD. These patients were matched using the same propensity score–based process to 1219 CHD controls contributing data to three consecutive 90-day periods relative to study entry.

As a direct result of doubling treatment time on converting to INHD, there was a sustained significant increase from 1.4 to 2.3 in mean eKt/V, accompanied by sustained significant decrease in ultrafiltration rate (UFR) from 11 to 6 ml/kg per min comparing period 1 with both periods 2 and 3 (Figure 4, A and B). These changes in eKt/V and UFR were not evident in propensity score–matched controls ($P<0.001$). Although INHD patients remained heavier than CHD patients ($P<0.001$), there was a trend for declining postdialysis weights and predialysis systolic blood pressure in both INHD and CHD (Figure 4, C and D). However, we observed a balanced increase in both interdialytic weight gain (IDWG) and intradialytic weight loss for INHD patients that was not evident in CHD patients (Figure 4, E and F).

Among laboratory biomarkers (Figure 5, A–E), a sustained, statistically significant decline in phosphorus levels from 5.73 to 5.02 mg/dl ($P<0.001$) was observed with conversion to INHD, whereas matched period prevalent CHD controls' phosphorus levels increased minimally during the follow-up

Table 2. Treatment parameters for 726 patients initiating therapy with INHD and their hemodialysis prescriptions during the immediate period before converting from CHD

Treatment Parameters (Mean [SD] or Percent)	In-Center Chronic Hemodialysis	
	Nocturnal	Prior Conventional
Time (min)	471 (31)	226 (28)
Blood flow rate (ml/min)	313 (77)	380 (69)
Dialysate flow rate (ml/min)	498 (143)	632 (135)
Dialyzer surface area (%)		
1.5 m^2	68	46
1.8 m^2	27	41
2.0 m^2	4	6
Other dialyzers	0.4	7.6

period from 5.75 to 5.85 mg/dl (P=0.01). A small, statistically significant decline was observed in white blood cell count, but values at each period were not significantly different from CHD controls. Patients on INHD began with slightly lower baseline hemoglobin and albumin than CHD controls but subsequently, had slightly higher levels during follow-up. Patients on CHD had smaller increases in albumin (0.2 versus 0.6 g/L) and hemoglobin (0.1 versus 0.4 g/dl), but there were no significant differences between INHD and CHD cohorts during each time period. For calcium, a small 0.1–0.2 mg/dl sustained, significant ($P<0.001$) increase of mean serum calcium was observed in the INHD cohort, with minimal change in CHD controls.

Technique Survival

Technique survival during the 2-year follow-up period is shown in Figure 6. The mean time on INHD was 410±256 days (median=401 days) during the follow-up period. Overall, 438 of the original 746 patients (59%) in our INHD cohort remained active on dialysis within Fresenius Medical Care, North America (FMCNA) at the 2-year time point less deaths/withdrawals (19%), renal transplants (12%), and discharges (10%). Among the active patients, 186 patients (42%) were still on INHD therapy after 2 years. To provide contrast, 1185 patients (57%) remained active among the CHD cohort at the end of the study less deaths/withdrawals (27%), renal transplants (6%), and discharges (10%).

DISCUSSION

To our knowledge, this study is the largest INHD survival study reported, with a longer follow-up period of up to 2 years. Results indicated a 25% lower adjusted mortality HR for patients on INHD therapy that was sustained over 2 years. This study followed INHD patients from the time of initial conversion and attempted to find suitable controls with a rigorous propensity score match that included case mix, vascular access, and key laboratory parameters, with additional matching by geographic area to account for local practice patterns and environmental/population factors and then by incident or prevalent patient status to avoid an imbalance between cohorts among patients new to dialysis therapy. Additionally, because there remained three measured factors that were not statistically balanced after the match, we performed second-stage Cox models to adjust for the remaining residual differences. Furthermore, the results were robust to sensitivity analyses that censored patients after 30 days of switching modality. Posthoc, despite adjusting for body mass index in the second-stage Cox model for mortality, we added baseline weight (which had a wider difference relative to what was reflected by the BMI) to the model, and results were minimally attenuated (data not shown).

Our findings extend outcome differences observed in our initial report, which only tracked a period-prevalent cohort over 1 year. In that study, the observed mortality was lower in the INHD cohort, but the difference lost statistical significance after adjustment for case mix and laboratories.[15] The initial report was designed as a 1-year overview of the program and suffered from numerous design flaws that were addressed in the current study. Since then, a prospective trial was undertaken by Ok et al.[16] that matched 247 INHD patients with 247 period-prevalent CHD patients based on age, gender, and presence of diabetes, finding a 72% relative risk reduction for mortality in the INHD cohort (P=0.02) over a mean follow-up period of 11.3±4.7 months. No other controlled INHD survival data have been published, although outcomes reported for nocturnal home hemodialysis (albeit not directly comparable because of different site and frequency of 5–7 times per week) indicated similar outcomes.[17,18] G. Nesrallah *et al.* (unpublished data) have shown a 45% mortality risk reduction (P=0.01) comparing home nocturnal hemodialysis with CHD. In comparison, we found a relatively modest but significant 27% relative risk reduction at 1 year and 25% by the second year of the follow-up period.

Almost by definition, in addition to daytime versus nighttime therapy, doubling of mean treatment time from 226 to 471 minutes differentiates CHD from INHD. Longer treatment time has been associated with improved outcomes.[7] The first directly relatable effect was a marked increase in urea clearance (Figure 4A), represented by eKt/V—with emphasis on the t component, despite the shift to lower K from prescriptions of dialyzers with less surface area and lower blood and dialysate flow rates (Table 2). However, urea clearance does not represent clearance of all solutes, especially those solutes that have larger molecular weight and/or are not as freely diffusible between body compartments.[19]

The most dramatic impact that we observed was on phosphorus (Figure 5C), consistent with nearly all studies of INHD,[8–11,13–16] driven by longer time for rate-limited equilibration of phosphate from nonvascular body compartments to the dialyzable vascular space to occur.[14,20] High levels of phosphorus have been associated with increased morbidity and mortality in epidemiologic studies of HD patients.[21,22] Of note, there were small, statistically significant changes in

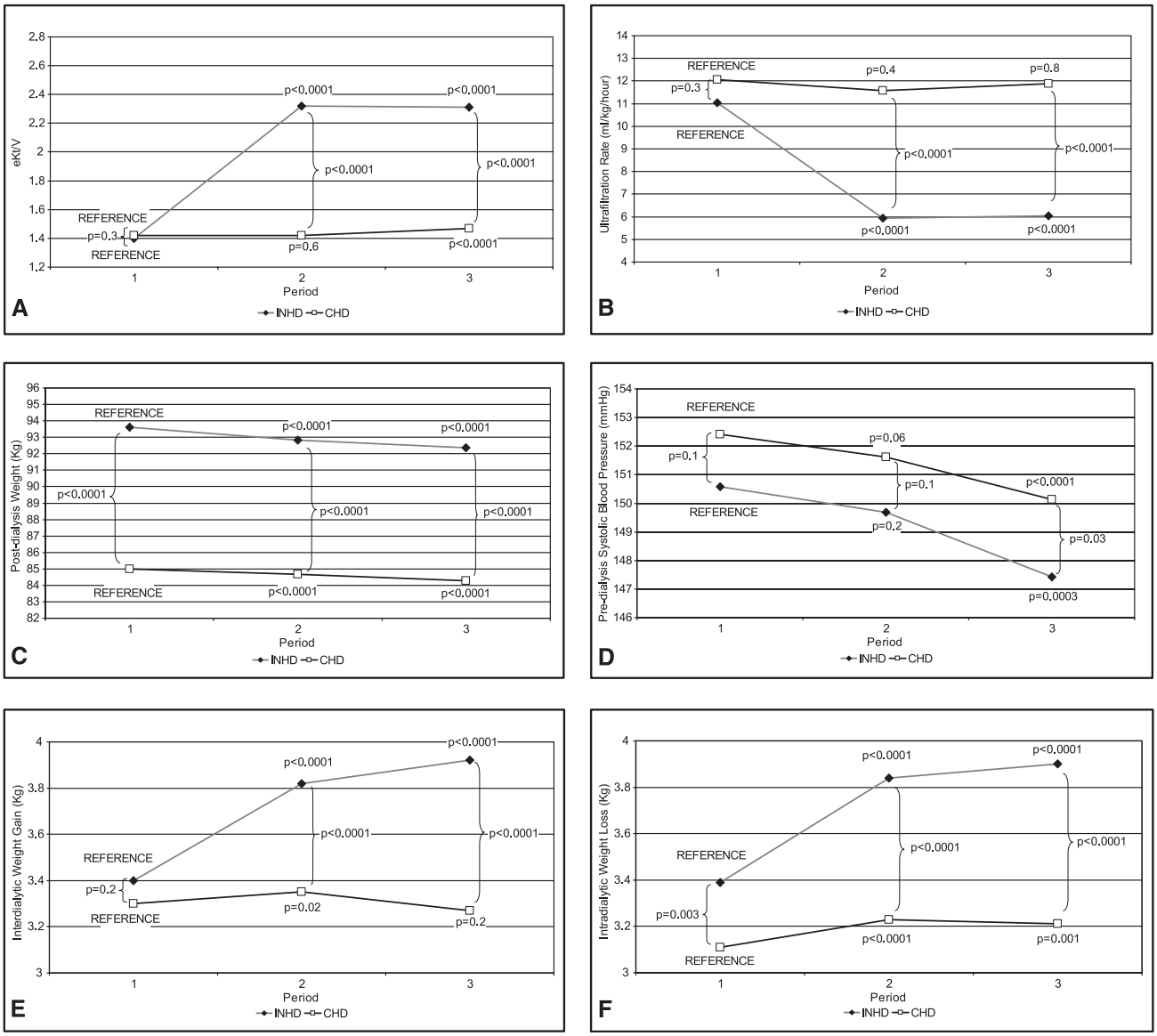

Figure 4. Improved clinical features on INHD. Changes in (A) dialysis dose, (B) ultrafiltration rate, (C) postdialysis weight, (D) predialysis systolic blood pressure, (E) interdialytic weight gain, and (F) intradialytic weight loss associated with conversion from CHD to INHD from baseline (period 1), first 90 days (period 2), and days 91–180 (period 3) along with period prevalent propensity score-matched controls that were treated solely with CHD. (INHD: *n*=435; CHD: *n*=1219).

other biomarkers, although their clinical significance is uncertain. Nevertheless, the direction of change in most of these biomarkers with INHD was either neutral or desirable. Among them, small differences in albumin between cohorts have been correlated with better morbidity and mortality.[23] In addition, an increase in serum calcium, as long as it does not lead to hypercalcemia, may be salutary, because low calcium levels have also been associated with higher mortal risk, particularly in African American patients.[24]

The other, more important major change directly attributable to doubling of treatment time was that INHD patients were able to remove accumulated fluid gains over a longer period, effectively reducing UFR by almost one-half (Figure 4B). Some INHD programs are actually used by referring physicians to address the needs of patients with difficulty removing fluid, often associated with high IDWG,[8,15] which is a potential explanation for proportionately higher representation of younger age, African American, and male in the INHD cohort. To date, at least three studies have shown better survival with lower UFR, with the threshold for increased mortal risk observed between 10 and 13 ml/kg per hour.[25–27] High UFRs predispose patients to myocardial ischemia and stunning from hypoperfusion related to intradialytic hypotension and tachycardia, especially in a patient with pre-existing myocardial disease.[28] Therefore, a pathobiologic link exists between UFR and cardiovascular morbidity and mortality.

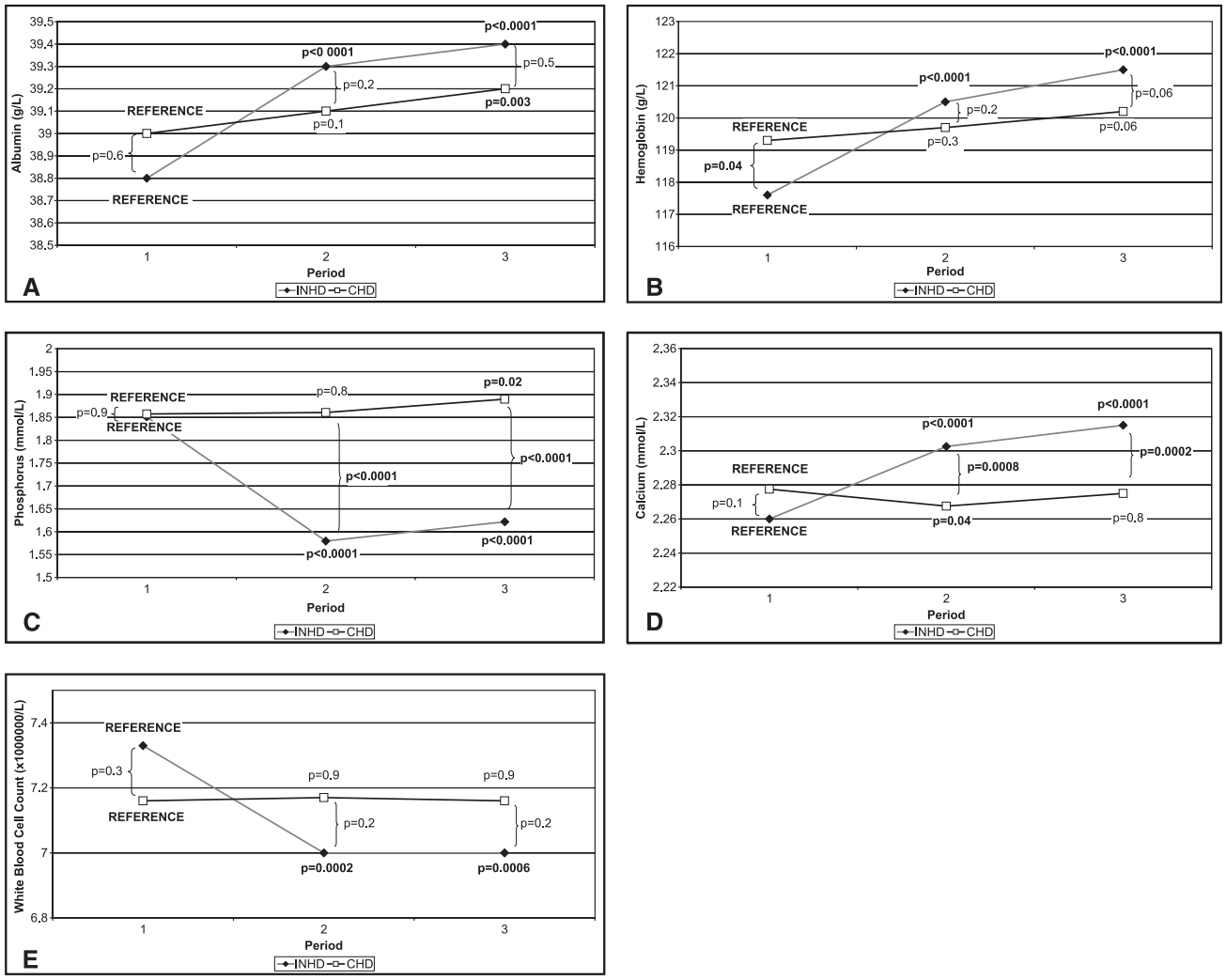

Figure 5. Improved biomarkers on INHD. Laboratory changes for (A) albumin, (B) hemoglobin, (C) phosphorus, (D) calcium, and (E) white blood cell count associated with conversion from CHD to INHD from baseline (period 1), first 90 days (period 2), and days 91–180 (period 3) along with period prevalent propensity score–matched controls that were treated solely with CHD. (INHD: *n*=435; CHD: *n*=1219).

The study has several limitations. First, the observational design delineates associations but does not prove causation. Hence, unmeasured residual confounding is unavoidable (*i.e.*, traits that may predispose patients to self-select nocturnal therapy, such as being educated or employed, may predispose to good outcomes). For example, residual confounding could be manifested by the higher transplantation rate observed in the INHD cohort, although it is also possible that extended survival may have allowed for a greater number of renal transplants to occur. A second limitation may be the lack of adjustment for patient comorbidity other than diabetes. Third, the study is subject to survival bias associated with selecting patients who are not all new to dialysis. However, we attempted to mitigate this issue by including dialysis vintage in the initial propensity score-matching algorithm, further matching by incident patient status based on dialysis vintage≤90 days versus vintage>90 days and then adjusting for vintage in the second-stage Cox models. Finally, the mortality rates observed in the control group (15% in the first year) were better than overall prevalent dialysis mortality rates of ~21% reported in the United States for 2008,[29] consistent with having a selected population—younger, mostly male, proportionately more African Americans, and larger body mass index. Anecdotally, many physicians have informally communicated to FMCNA staff that patients with high ultrafiltration requirements (because of high IDWG, often in large patients) were preferentially referred for INHD. These patients' estimated dry weights were difficult to achieve within the constraints of conventional dialysis; at times, this difficulty led to symptomatic treatments because of intravascular volume depletion, if not overt hypotension, from high rates of fluid removal. Such patient selection patterns also highlight that preference for INHD therapy is not necessarily for everyone.[4]

In summary, notwithstanding the possibility of residual selection bias, patients who opted for or converted to INHD

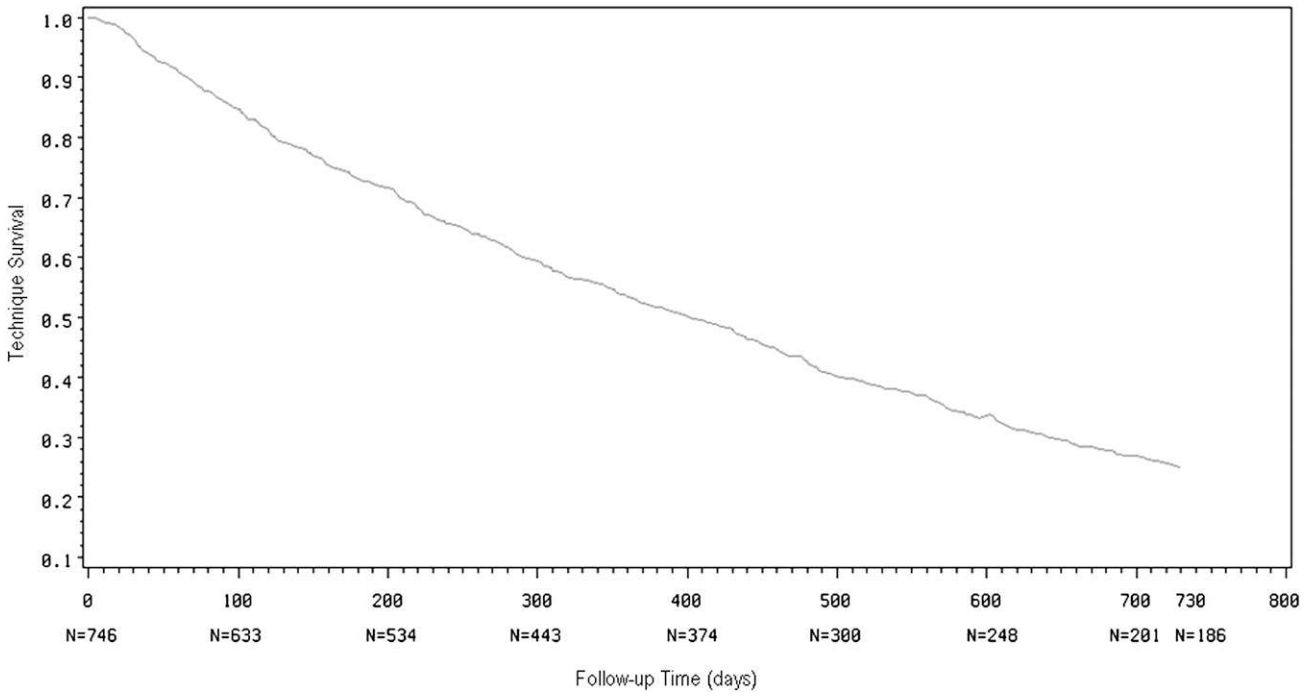

Figure 6. Long-term maintenance INHD therapy. INHD technique survival over 2 years.

exhibited a 25% reduction in 2-year mortality risk compared with rigorously matched controls on CHD from within the same geographic area. Conversion to INHD was associated with favorable laboratory biomarkers with significantly lower serum phosphorus despite improved or stable nutritional status (reflected by stable or higher serum albumin, stable or higher IDWG, and stable or minimally lower postdialysis weight). This study supports the notion that therapy with INHD is a viable alternative dialysis regimen. The potential role of extended treatment time on solute and fluid clearance (and equilibration in body compartments) that may explain our findings requires additional evaluation. A randomized clinical trial is warranted (*e.g.*, three times per week in-center nocturnal 4- vs. 8-hour HD treatments), but the feasibility of conducting such a study has yet to be formally explored.

CONCISE METHODS

Patient Population

All consecutive patients initiating >5.5-hour INHD for the first time from 77 FMCNA facilities between January 1, 2006 and December 31, 2007 were eligible. All other CHD patients from up to 288 facilities within the surrounding geographic area that were active on January 1, 2007, were eligible to become controls. We collated demographic (age, gender, race, diabetes, length of time on dialysis or vintage, body mass index as derived from postdialysis weight and height, and vascular access) and baseline laboratory information (albumin, hemoglobin, phosphorus, calcium, and white blood cell count) immediately before conversion to INHD. These baseline variables were used to construct a propensity score. The final study cohorts consisted of a 1:3 ratio of matched INHD to CHD patients (Figure 1) based on three matching factors: propensity score, geographic area (*i.e.*, facility location), and incident patient status (*i.e.*, dialysis vintage≤90 days versus vintage>90 days).

In FMCNA facilities, HD treatments generally used Fresenius 2008H/K machines and single use of Optiflux 160, 180, or 200 dialyzers (Fresenius USA, Walnut Creek, CA) with few exceptions. Treatment parameters that differentiated INHD from CHD included longer dialysis time, smaller dialyzer surface area, and lower blood and dialysate flow rates.[15] For the current study, we documented dialysis prescription changes in these parameters on conversion from CHD to INHD. All blood samples were drawn predialysis (except postdialysis urea for dialysis dose calculations) and were processed by a central laboratory (Spectra Laboratories, Rockleigh, NJ).

Study Endpoints

The study entry date was defined as the conversion date to INHD therapy, and for CHD controls, the midpoint of the eligibility period (January 1, 2007) was the study entry date. All patients were followed for up to 2 years until December 31, 2009, with the primary endpoint being mortality (a composite of death and withdrawal from dialysis). Patients lost to follow-up during the year contributed exposure time until kidney transplant or the last day before transfer out of the FMCNA system. Technique failure rate, defined by the proportion of active dialysis patients that converted to CHD, home HD, or peritoneal dialysis for at least 30 days, was also recorded as a secondary endpoint.

Statistical Analyses

Descriptive data at baseline were presented as means or percentages of the total. Statistical significance was determined based on *t* tests and chi-squared tests where appropriate. We plotted Kaplan–Meier survival curves for each cohort. Cox proportional hazard regression models were used to determine HR for both 1- and 2-year mortality comparing INHD with matched CHD controls. The proportional hazard assumption was tested and found to be valid. Patients were analyzed based on treatment assignment at the start of follow-up, regardless of whether they received the same dialysis throughout the follow-up period (*i.e.*, by intention to treat). Second-stage Cox models included additional adjustment for age, vintage, and body mass index, because these variables exhibited residual differences after the propensity score–based matching process. Consistent with prior analyses, vintage was transformed into square root when entered into the models.[21] We performed a sensitivity analysis where patients were censored on changing dialysis modality for greater than 30 days (as-treated analysis). Deaths occurring within 30 days of censor date, however, were attributed to baseline modality.

In the subset of INHD patients with CHD data available from up to 90 days before conversion and with follow-up data for up to 180 days of INHD therapy, we evaluated the early changes (mean value within the first 90 days) and sustained changes (91–180 days) in postdialysis weight, IDWG, intradialytic weight loss, predialysis systolic blood pressure, UFR based on the intradialytic change in weight (ml/kg body weight per hour), and laboratory results (albumin, hemoglobin, phosphorus, eKt/V, white blood cell count, and calcium). Albumin was determined by bromcresol green method, whereas eKt/V was derived from Kt/V obtained by urea kinetic modeling based on two-sample blood urea nitrogen variable volume method.[21,30] For CHD patients matched to this INHD subgroup, we also obtained the corresponding mean baseline (90 days before study entry), first 90 days, and 91–180 days follow-up data. These variables were all continuous variables that were compared using two-sided *t* tests in two ways: (*1*) changes relative to the baseline and (*2*) period-matched values between INHD and CHD cohorts. All statistical tests were performed using SAS version 9.2 (SAS Institute, Cary, NC).

ACKNOWLEDGMENTS

We are grateful to Sandra MacGregor for judiciously compiling information about the FMCNA nocturnal in-center programs. We also thank Weiling Wang for conducting posthoc statistical analyses that were requested during peer review. We thank Allison Baginsky and Carol-Ann McKenna for preparing print-quality figures. Finally, we thank the clinical staff caring for our patients, especially the staff that works the night shift and maintains excellent quality of care for patients on INHD therapy.

Part of this material was presented in the National Kidney Foundation's 2010 Spring Clinical Meeting in Orlando, Florida, April 15–17, 2010.

DISCLOSURES

E.L., J.X., K.L., N.O., M.L., and R.M.H. were or remain as employees of Fresenius Medical Care, North America, and may have stock options.

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