



## **Survival and hospitalization among patients using nocturnal and short daily compared to conventional hemodialysis: a USRDS study**

Kirsten L. Johansen, *University of California San Francisco*

[Rebecca Zhang](#), *Emory University*

[Yijian Huang](#), *Emory University*

Shu-Cheng Chen, *USRDS Coordinating Center*

Christopher R. Blagg, *Northwest Kidney Centers*

Alexander S. Goldfarb-Rumyantzev, *Harvard University*

Christopher D. Hoy, *Rubin Dialysis Center*

Robert S. Lockridge, *Lynchburg Nephrology Dialysis, Inc.*

Brent W. Miller, *Washington University*

Paul Eggers, *National Institute of Diabetes and Digestive and Kidney Diseases*

*Only first 10 authors above; see publication for full author list.*

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## Survival and hospitalization among users of short daily and nocturnal hemodialysis versus propensity-matched controls: a USRDS study

Kirsten L. Johansen, MD<sup>1,2</sup>, Rebecca Zhang, MS<sup>1</sup>, Yijian Huang, PhD<sup>1</sup>, Shu-Cheng Chen, MS<sup>3</sup>, Christopher R. Blagg, MD<sup>4</sup>, Alexander S. Goldfarb-Rumyantzev, MD<sup>5</sup>, Christopher D. Hoy, MD<sup>6</sup>, Robert S. Lockridge Jr, MD<sup>7</sup>, Brent W. Miller, MD<sup>8</sup>, Paul Eggers, PhD<sup>9</sup>, and Nancy G. Kutner, PhD<sup>1</sup>

<sup>1</sup>USRDS Rehabilitation/QoL Special Studies Center, Emory University, Atlanta, GA

<sup>2</sup>Nephrology Section, San Francisco VA Medical Center and Division of Nephrology, University of California, San Francisco, CA

<sup>3</sup>USRDS Coordinating Center, Minneapolis, MN

<sup>4</sup>Northwest Kidney Centers, Seattle, WA

<sup>5</sup>Harvard Medical School, Boston, MA

<sup>6</sup>Rubin Dialysis Center, Saratoga Springs, NY

<sup>7</sup>Lynchburg Nephrology Dialysis, Inc, Lynchburg, VA

<sup>8</sup>Washington University School of Medicine, St. Louis, MO

<sup>9</sup>National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

### Abstract

Little is known about survival and hospitalization among alternative-regimen hemodialysis (HD) users compared to thrice-weekly conventional HD patients who have similar characteristics and medical histories. We conducted a cohort study of alternative-regimen HD users and propensity score (PS)-matched controls. Collaborating clinicians identified 101 patients in their programs who used nocturnal HD (NHD) and 44 patients who used short daily HD (SDHD) for 60 days or more. Ten PS-matched control patients for each NHD and SDHD patient were identified from the United States Renal Data System database. Primary outcomes were risk for all-cause mortality and risk for the composite outcome of mortality or major morbid event (AMI or stroke), investigated in Cox proportional hazards models. Risks for all-cause, cardiovascular-related, infection-related, and vascular access-related hospital admissions were also explored. NHD was associated with reduced mortality risk (HR 0.34; 95% CI, 0.21-0.58;  $P < 0.0001$ ) and with reduced risk for mortality or major morbid event (HR 0.49; 95% CI, 0.31-0.78;  $P = 0.003$ ) compared to controls.

Correspondence: Nancy Kutner, PhD, Department of Rehabilitation Medicine, Emory University, 1441 Clifton Road NE, Atlanta, GA 30322, USA. Phone: 404-712-5561 Fax: 404-712-5805, nkutner@emory.edu.

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**There was a reduced but non-significant** risk of death for patients using SDHD compared to controls (HR 0.61; 95% CI, 0.30-1.24;  $P=0.17$ ). All-cause and specific hospitalizations did not differ significantly between NHD and SDHD patients and their matched control cohorts. This study provides additional evidence that NHD may improve patient survival.

## Keywords

Daily hemodialysis; hospitalization; survival; USRDS

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**In the United States**, the number of programs offering nocturnal HD therapy (NHD) is reported to have increased from 73 in 2004 to 300 in 2008, and the number of programs offering short-duration daily HD therapy (SDHD) is reported to have increased from 37 in 2004 to 480 in 2008.<sup>2</sup> There is great interest in the outcomes of patients undergoing **these alternative** HD regimens, which are believed to be more physiological and better tolerated by patients than conventional thrice-weekly HD.

**Alternative** HD regimens have the potential to increase longevity and reduce hospitalization as compared to conventional HD (CHD). Unfortunately, selection bias has confounded many reports on outcomes associated with **alternative** HD regimens.<sup>3-8</sup> There is little information about survival and hospitalization outcomes among users of **alternative** HD regimens compared to controls who have similar demographic characteristics and medical histories.

We used the USRDS database to examine mortality and hospitalization outcomes for patients from multiple programs who used NHD or SDHD for at least 60 days, compared to outcomes for patients with similar characteristics treated by thrice-weekly CHD who were identified by propensity score (PS) matching from the USRDS database. We examined outcomes separately for patients using NHD and SDHD because these are not equivalent therapies.<sup>9</sup> The primary research question was the risk for mortality among NHD users compared to CHD controls and among SDHD users compared to CHD controls. We also investigated a composite outcome of risk for mortality or a major morbid event, i.e. acute myocardial infarction (AMI) or stroke, as recommended by Chertow,<sup>1</sup> and explored risks for all-cause and specific types of hospitalization.

## Results

Approximately 60% of both NHD and SDHD patients dialyzed 6 days/week, with most of the remaining patients dialyzing 5 days/week (Table 1). All NHD and SDHD patients dialyzed at home; 1% of CHD patients used home HD as of January 1, 2003. Most patients converted to an **alternative** HD regimen from conventional center HD or conventional home HD; two patients converted from continuous ambulatory peritoneal dialysis and continuous cycling peritoneal dialysis, respectively. The mean age at which patients switched to NHD therapy was 52.3 (range 23-81) years, and the mean age at which patients switched to SDHD therapy was 48.2 (range 14-78) years. Patients used NHD or SDHD for a median of 1,102 days (approximately 3 years).

NHD patients and controls were similar on all variables used for PS matching (Table 2). SDHD patients and PS-matched controls were also similar on all variables used for PS matching (Table 2). The majority of patients in both **alternative-regimen** HD cohorts were male and white. Few patients who initiated **alternative** HD regimens were characterized by lower income, based on Medicaid coverage at treatment start as an indicator of financial status. Both cohorts had a low average number of cardiovascular conditions at start of ESRD treatment, but patients who initiated NHD were more likely than patients who initiated SDHD to have coronary artery disease at treatment start.

**The observed mortality rates for NHD controls and SDHD controls were 147 and 138, respectively, per 1,000 patient years. For NHD patients and SDHD patients, the respective observed mortality rates were 70 and 90 per 1,000 patient years.**

Multivariable Cox proportional hazards regression analyses indicated that NHD compared to CHD was associated with a significantly reduced hazard for death (hazard ratio 0.34; confidence interval 0.21 to 0.58;  $P < 0.0001$ ) [Table 3]. There was a reduced **but non-significant** risk of death for SDHD compared to CHD (hazard ratio 0.61; confidence interval 0.30 to 1.24;  $P = 0.17$ ) [Table 3]. Corresponding results from Kaplan-Meier analyses of survival among NHD patients and CHD controls, and survival among SDHD patients and CHD controls, are shown in Figure 1 and Figure 2, respectively. Additional multivariable Cox proportional hazards regression analyses indicated that NHD compared to CHD was associated with a significantly reduced hazard for death or major morbid event, i.e. AMI or stroke (hazard ratio 0.49; confidence interval 0.31 to 0.78;  $P = 0.003$ ). Among SDHD users the hazard ratio for death or major morbid event compared to CHD was 0.73; confidence interval 0.37 to 1.44;  $P = 0.36$ .

Multivariable Cox regression analyses did not show that NHD or SDHD was associated with significantly reduced hazard for all-cause hospitalization, non-vascular access-related hospitalization, cardiovascular hospitalization, or infection-related hospitalization. For hospitalization associated with congestive heart failure specifically, the hazard ratio for NHD compared to CHD was 0.59; confidence interval 0.29 to 1.20;  $P = 0.15$ , and the hazard ratio for SDHD compared to CHD was 0.83; confidence interval 0.26 to 2.68;  $P = 0.75$ . For vascular access-related hospitalization, the hazard ratio for NHD compared to CHD was 1.34; confidence interval 0.91 to 1.97;  $P = 0.14$ , and the hazard ratio for SDHD compared to CHD was 0.70; confidence interval 0.31 to 1.60;  $P = 0.40$ .

## Discussion

Our study demonstrated a survival benefit of NHD compared to CHD in a relatively modern cohort assembled from multiple centers in the US in which most patients received NHD 5 nights per week. Our results are in general agreement with those of Charra *et al.*,<sup>10</sup> who compared the survival of patients receiving thrice weekly NHD to that of registry patients receiving CHD in Japan, Europe, and the US. The overall 87% survival of the Charra *et al.* cohort was superior to any of the registries, and the advantage was particularly marked for older patients. Pierratos *et al.*,<sup>11</sup> in a report of 5-year outcomes among 30 patients treated with frequent NHD delivered at home, noted a mortality rate of 2.4% per year, a rate that is substantially lower than that reported by the US Renal Data System for the general HD

population.<sup>12</sup> [Check Pierratos paper to see if this was their conclusion. Can't really compare this rate directly to ours.]

The improved survival associated with NHD is biologically plausible. Both of the high intensity dialysis cohorts in our study had an apparent immediate survival benefit that could be in part related to patient selection. However, for the NHD cohort, the survival curves continue to diverge throughout the entire follow-up period (Figure 1), suggesting a possible treatment effect. Multiple clinical benefits associated with high intensity HD have been documented. Many of these benefits would be expected to enhance survival, including reduction in left ventricular hypertrophy,<sup>16-18</sup> correction of sleep apnea,<sup>19</sup> and improved control of hypertension, mineral metabolism, endocrine abnormalities, and anemia.<sup>20,21</sup> Improvements in blood pressure,<sup>6,22</sup> hemoglobin,<sup>23</sup> homocysteine,<sup>24</sup> calcium/phosphorus product,<sup>6</sup> and Kt/V,<sup>22</sup> as well as patient-assessed quality of life<sup>6,22</sup> have been identified in patients using high intensity HD by clinicians who contributed to this study.

The current analysis shares some of the limitations of prior studies, including low power as previously mentioned as well as potential confounding resulting from patient selection. Although patient selection strategies differ across centers and over time, they are clearly evident in most reports of high intensity dialysis strategies. Patients starting NHD or SDHD who were identified for our study were younger, less likely to be lower income and less likely to have diabetic ESRD than the overall HD population in the U.S., and were characterized by fewer cardiovascular comorbidities than patients in the overall HD population (data not shown). We used PS matching to identify CHD control patients with demographic, clinical and hospitalization history characteristics similar to high NHD and SDHD users in each of these cohorts. We believe that our propensity score matching, and in particular the incorporation of matching based on prior hospitalization rates, is a significant advance over previous attempts to compare outcomes between patients receiving high intensity dialysis and those receiving CHD. Furthermore, the matching strategy was successful in that it resulted in control groups with similar vintage and prior hospitalization rates. Nevertheless, any matching strategy is only as good as the data available upon which to match, and patients who are considered appropriate for a home-based regimen such as NHD are likely to be different than in-center dialysis patients receiving CHD, raising the strong possibility of residual confounding. Specifically, we lacked data on several important potential predictors of survival and hospitalization, such as type of vascular access, recent laboratory parameters, and patient adherence to dialysis. However, it is important to consider that, although the select nature of patients appropriate for home dialysis makes them difficult to compare to CHD patients, these selection issues reflect actual practice and are not likely to disappear even if a concerted effort is made to increase the use of high intensity dialysis. Similar to peritoneal dialysis, it is likely that a majority of home-based intensive dialysis therapy users will be younger and more stable and have higher socioeconomic status than in-center dialysis patients.

We did not find significantly better survival among SDHD patients when compared to PS-matched CHD control subjects. However, the point estimate of the hazard ratio is in accord with data from Kjellstrand *et al.*<sup>13</sup> and Blagg *et al.*,<sup>14</sup> who reported a lower mortality on SDHD after adjustment for age, sex, race, and the presence of diabetes. Possible reasons for

the lack of significantly prolonged survival in our cohort include low statistical power due to the smaller sample size of our study and the low event rate in the control group because of the additional adjustment provided by the propensity score matching that included such factors as pre-conversion hospitalization rates and days. The SDHD cohort assembled for this investigation was in fact younger and healthier than the general US dialysis population, as evidenced by their very low pre-conversion hospitalization rates. Similarly, we did not detect a reduction in hospitalization rates related to changing to either SDHD or NHD, contrary to reports by Ting *et al.*<sup>5</sup> for SDHD and several groups of investigators for NHD,<sup>6,7,11,15</sup> all of which included fewer patients than the current investigation. We believe that patient selection could be an important factor limiting our ability to detect changes in hospitalization. Our SDHD and NHD cohorts both had lower hospitalization rates in the year preceding the switch to high intensity dialysis than did previously described cohorts,<sup>5-7,11,15</sup> making it less likely that hospitalization would be reduced by intensifying dialysis therapy and limiting power to detect such a change even if present.

The possibility that high intensity HD may be associated with an increase in vascular access complications due to more frequent cannulation has been a concern. Prior evidence about this issue has been equivocal.<sup>25</sup> Our results, as well as results from other recent studies, do not indicate that a significant increase in vascular access complications requiring hospitalization accompanies use of high intensity HD. In an RCT recently reported by Culleton *et al.*,<sup>18</sup> complications related to vascular access did not differ significantly over a six-month follow-up between patients randomized to NHD and patients randomized to CHD. In our study, risk for vascular access-related hospital admissions was not significantly associated with NHD use or SDHD use compared to matched controls. The proportion of hospitalization events that were vascular access-related remained a small proportion of the total hospitalization events observed for high intensity dialysis patients, limiting power to detect changes related to treatment type. Furthermore, many vascular access events may be managed without hospital admission and are not counted in these data, making it impossible to rule out an increase in vascular access events.

Vascular access type is an especially important potential confounder because it is clearly associated with survival – better in the case of arteriovenous fistula and worse in the case of tunneled catheter<sup>26-29</sup> – and because access type may also be associated with selection for high intensity dialysis. Some groups initially required or preferred tunneled dialysis catheters for NHD. However, a recent report from the International Quotidian Dialysis Registry shows that all types of dialysis access are now in use for high intensity dialysis.<sup>30</sup> In this registry, the prevalence of catheter use is 21.1% among patients from the US receiving SDHD at home and 24.6% for patients receiving NHD at home. These numbers are similar to what has been reported in the US CHD cohort from the Dialysis Outcomes and Practice Patterns Study (DOPPS), which varied from 17% during DOPPS I (1996-2000) to 27% in DOPPS II (2002-2003).<sup>31</sup> Thus, it does not appear that there is a large difference in access type between patients receiving alternative and conventional dialysis therapies at the national level. However, it is possible that there could be differences between our alternative dialysis and CHD cohorts since this variable was not available for matching.

There is evolving variation in frequency, duration, and setting of treatments. For example, compared to the treatment patterns described in Table 1, it is likely that the median number of SDHD sessions/week is now 6 rather than 5, and NHD patients may be more likely to have 5 rather than 6 sessions/week in order to avoid phosphorus depletion. The International Quotidian Dialysis Registry, developed to track treatment and outcomes in the high intensity dialysis population, has recognized this heterogeneity and has classified patients into five different categories based on treatment length, frequency, and location.<sup>30</sup> Thus, although heterogeneity in regimens makes it difficult to compare alternative dialysis regimens with CHD in large numbers of patients, it is reflective of current clinical practice. Furthermore, the heterogeneity in treatment regimens would be likely to obscure rather than exaggerate any differences in survival or hospitalization by increasing variability within the high intensity groups.

A RCT, such as the ongoing Frequent Hemodialysis Network randomized trials of NHD and SDHD, would provide the most definitive evidence about survival benefit associated with high intensity HD. However, these studies are not powered to examine mortality outcomes, and recruiting the number of patients needed for such a study is not considered feasible.<sup>33</sup> Given that large-scale trials on alternative-regimen HD vs. CHD may never be conducted,<sup>34</sup> observational studies can provide important insight. Culleton et al. recommend that data collection for hospitalizations and vascular access complications should have high priority in future observational studies.<sup>18</sup> In addition, evolving technology for frequent HD requires study, as new machines become available and practice standards evolve.<sup>33</sup> In the meantime, our study adds to existing evidence that NHD **may improve** patient survival, which remains the ongoing primary challenge in provision of dialysis therapy.<sup>1,33</sup>

## Methods

### Data sources and collection

Eight clinicians with substantial **high intensity** HD programs were asked in to participate in a special USRDS linked data study. Three of these clinicians expressed interest in the study but decided not to participate due to reported difficulties in obtaining institutional review board approval and/or lack of administrative help needed to furnish the data requested for the study. Requests were also circulated to attendees of the 2001 NIH Daily Dialysis Workshop, but these requests did not yield any additional participants. Thus, five clinicians provided data to the USRDS Coordinating Center for patients who had undergone **high intensity** HD in their programs over the time period of 1997 to 2005. These datasets included information about the type of frequent HD used (NHD or SDHD), number of days/week treatment, number hours/HD session, start date of frequent HD, and end date if applicable. This paper analyzes outcomes for 101 patients who used NHD and 44 patients who used SDHD for more than 60 days. Most of the SDHD patients used the PHD™ System (Aksys Ltd., Lincolnshire IL).

The USRDS Coordinating Center deidentified the data by assigning unique USRDS patient identifiers before sending the dataset to the USRDS Rehabilitation/Quality of Life Special Studies Center at Emory University. Data for individual patients were then linked with information available in the updated 2007 USRDS Standard Analysis Files (SAFs). In





within a maximum of 365 days before baseline (start of frequent HD or 2003). The *c* statistic of the PS model predicting NHD use was 0.56, and the *c* statistic of the PS model predicting SDHD use was 0.60. We matched the 145 frequent HD patients to CHD patients in a 1:10 ratio. Among them, 129, 11, and 5 frequent HD patients were matched to CHD patients who had a PS that was identical to 4, 3, and 2 digits, respectively.

Baseline characteristics of patients who started NHD (n=101) and matched CHD controls (n = 1010) were compared by t test (continuous variables) and  $\chi^2$  test (categorical variables). Similarly, baseline characteristics of SDHD patients (n=44) and matched CHD controls (n=440) were compared by t test and  $\chi^2$  test. The association of dialysis modality (NHD vs. CHD; SDHD vs. CHD) with risk for death, risk for death or major morbid event (AMI, stroke), and risk for hospitalization (**all-cause, cardiovascular-related, CHF-related, infection-related, and vascular access-related**) was examined in multivariable Cox proportional hazards models. Observations were censored at transplantation or end of follow-up; in the exploratory analyses of risk for hospitalization, observations were also censored at death. For death, the follow-up date was September 30, 2006, the latest date for which mortality outcomes were available. For the composite endpoint (death or major morbid event, i.e. AMI, stroke) and for hospitalization outcomes, the follow-up date was December 31, 2005, the latest date for which hospitalization outcomes were available.

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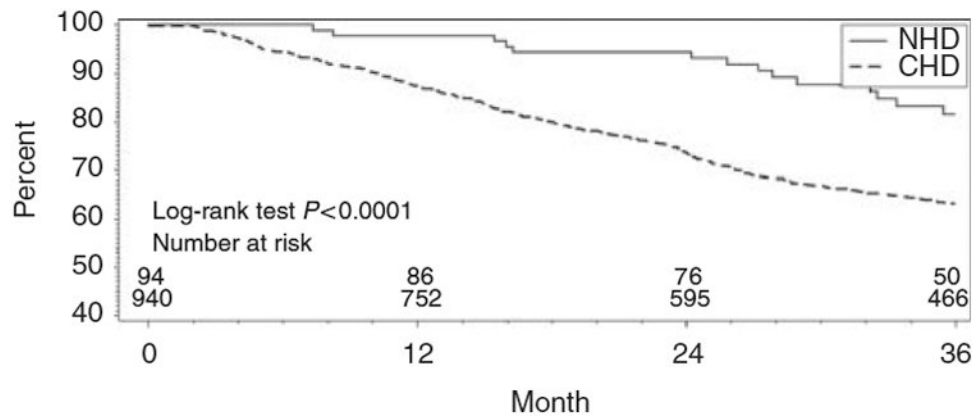
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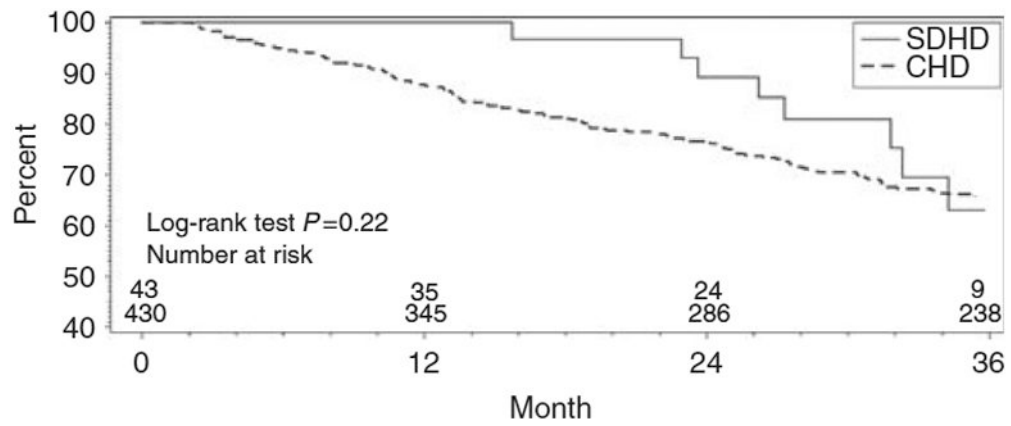
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**Figure 1. Kaplan–Meier analysis of nocturnal hemodialysis (NHD) therapy patient and conventional hemodialysis (CHD) control survival from baseline**  
Patient survival was analyzed as time until death; observations were censored at the end of follow-up or transplantation.



**Figure 2. Kaplan–Meier analysis of short-duration daily hemodialysis (SDHD) therapy patient and conventional hemodialysis (CHD) control survival from baseline**

Patient survival was analyzed as time until death; observations were censored at the end of follow-up or transplantation.

**Table 1**  
**Dialysis treatment characteristics**

	NHD (n=101)	SDHD (n=44)	CHD*
Session time (h)			
Mean (SD)	7.2 (0.66)	2.9 (0.58)	3
Median	7	2.83	
Range	(4.5, 8)	(1.67, 4)	(2.5, 4)
Sessions per week (d)			
Mean (SD)	5.6 (0.68)	5.4 (0.54)	3.5
Median	6	5	
Range	(3, 6)	(4, 6)	(2, 4)
Blood flow (ml/min; range)	200-300	250-500	250-500
Dialysate flow (ml/min; range)	200-300	300-800	500-800
Average Kt/V per session	1.10-1.80	0.38-1.26	1.12-1.75

Abbreviations: NHD, nocturnal hemodialysis; SDHD, short daily hemodialysis; CHD, conventional hemodialysis.

\* standard hemodialysis prescription

**Table 2**  
**Characteristics of NHD study cohort and CHD controls and characteristics of SDHD study cohort and CHD controls**

	NHD (N=101)	CHD Controls (N=1,010)	P	SDHD (N=44)	CHD Controls (N=440)	P
Age (yr, mean [SD]) <sup>*</sup>	47.6 (16.3)	48.0 (17.4)	0.83	41.2 (17.2)	42.0 (18.5)	0.78
Male (%)	65.4	67.1	0.72	72.7	75.5	0.69
Race (%)			0.93			0.79
Native American	0.0	0.0		0.0	2.7	
Black	23.8	23.4		20.5	20.0	
White	76.2	76.6		70.5	70.9	
Asian	0.0	0.0		6.8	4.6	
Other	0.0	0.0		2.3	1.8	
Medicaid coverage <sup>*</sup>	6.6	6.1	0.88	11.1	11.3	0.97
Number cardiovascular conditions (mean [SD]) <sup>*</sup>	0.6 (0.9)	0.5 (0.9)	0.57	0.4 (0.9)	0.3 (0.6)	0.70
CHF (%)	16.9	19.1	0.61	11.4	14.3	0.64
CAD (%)	22.5	15.7	0.10	11.4	6.6	0.28
CVD (%)	6.7	3.9	0.19	2.9	2.6	0.92
PVD (%)	6.7	7.4	0.82	5.7	3.7	0.56
BMI (mean [SD]) <sup>*</sup>	29.2 (8.5)	29.6 (8.6)	0.69	26.2 (7.3)	26.3 (6.8)	0.97
Diabetic ESRD (%)	27.0	25.8	0.81	25.0	25.8	0.92
Months on dialysis (mean [SD]) <sup>†</sup>	55.8 (66.4)	56.6 (61.6)	0.90	83.7 (87.1)	88.3 (82.6)	0.73
All-cause hospital admissions/person-year <sup>‡</sup>	1.1	0.9	0.55	0.6	0.7	0.64
All-cause hospital days/person-year <sup>‡</sup>	5.7	5.1	0.81	3.1	3.4	0.67
Cardiovascular admissions/person-year <sup>‡</sup>	0.4	0.3	0.52	0.1	0.1	0.87
Cardiovascular hospital days/person-year <sup>‡</sup>	1.9	1.5	0.70	0.4	0.4	0.98
Vascular access admissions/person-year <sup>‡</sup>	0.07	0.06	0.82	0.1	0.1	0.93
Vascular access hospital days/person-year <sup>‡</sup>	0.3	0.2	0.71	0.3	0.3	0.91

Abbreviations: NHD, nocturnal hemodialysis; SDHD, short daily hemodialysis; ESRD, end-stage renal disease; CHF, congestive heart failure; CAD, coronary artery disease; CVD, cerebral vascular disease; PVD, peripheral vascular disease; BMI, body mass index.

<sup>\*</sup> As of ESRD treatment start, recorded in Medical Evidence Form.

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<sup>†</sup>As of conversion to NHD or SDHD, for CHD patients, as of 1/1/03.

<sup>‡</sup>During 365 days prior to NHD or SDHD conversion; for CHD patients, during 365 days prior to 1/1/03.



**Table 3**  
**Multivariable Cox proportional hazards models predicting HD patient risk for mortality and risk for composite endpoint of mortality/major morbid event (AMI, stroke)**

Risk Factor	NHD cohort and controls		SDHD cohort and controls	
	All-cause mortality Hazard Ratio (95% CI)	Mortality/AMI, stroke Hazard Ratio (95% CI)	All-cause mortality Hazard Ratio (95% CI)	Mortality/AMI, stroke Hazard Ratio (95% CI)
Age (years)	1.04 (1.03, 1.05) <sup>*</sup>	1.04 (1.04, 1.05) <sup>*</sup>	1.04 (1.02, 1.05) <sup>*</sup>	1.04 (1.03, 1.05) <sup>*</sup>
Male	1.05 (0.85, 1.30)	0.98 (0.80, 1.21)	1.15 (0.81, 1.65)	1.21 (0.84, 1.75)
Black	1.12 (0.88, 1.44)	0.95 (0.75, 1.22)	1.04 (0.77, 1.40)	1.02 (0.75, 1.38)
Medicaid	1.31 (1.11, 1.53) <sup>‡</sup>	1.31 (1.12, 1.54) <sup>‡</sup>	1.64 (0.96, 2.79)	1.66 (0.94, 2.93)
Diabetic ESRD	1.45 (1.14, 1.85) <sup>‡</sup>	1.36 (1.07, 1.72) <sup>§</sup>	1.53 (1.07, 2.21) <sup>§</sup>	1.41 (0.97, 2.05)
No. cardiovascular conditions	1.00 (0.90, 1.12)	1.05 (0.94, 1.17)	1.06 (0.85, 1.32)	1.04 (0.83, 1.31)
BMI (kg/m <sup>2</sup> )	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	0.99 (0.95, 1.02)	1.01 (0.97, 1.04)
Months on dialysis	1.00 (0.999, 1.004)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.999, 1.005)
Frequent HD	0.34 (0.21, 0.58) <sup>*</sup>	0.49 (0.31, 0.78) <sup>‡</sup>	0.61 (0.30, 1.24)	0.73 (0.37, 1.44)

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; BMI, body mass index; HD, hemodialysis.

<sup>\*</sup>  $P < 0.0001$

<sup>†</sup>  $P < 0.001$

<sup>‡</sup>  $P < 0.005$

<sup>§</sup>  $P < 0.05$