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# A systematic review of the effect of nocturnal hemodialysis on blood pressure, left ventricular hypertrophy, anemia, mineral metabolism, and health-related quality of life

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**A systematic review of the effect of nocturnal hemodialysis on blood pressure, left ventricular hypertrophy, anemia, mineral metabolism, and health-related quality of life.**

*Background.* Nocturnal hemodialysis is a novel form of dialysis where patients perform dialysis 6 nights per week while they sleep. Multiple publications report significant improvements in selected clinical outcomes, although the strength of these results is limited by shortcomings in study design. A systematic review of the current available literature was undertaken to examine the effect of nocturnal hemodialysis on key health outcomes.

*Methods.* An inclusive search of medical databases was undertaken to identify all nocturnal hemodialysis studies. These results were manually reviewed for relevance to nocturnal hemodialysis and its impact on the following predefined health outcomes: blood pressure control, left ventricular hypertrophy, anemia, mineral metabolism, and health related quality of life. Case reports, short-term studies (<4 weeks), studies without comparator groups, and studies not reporting data in a quantitative fashion were excluded. The results of the remaining studies were reported in tabular format.

*Results.* Of the initial 270 studies identified, only 14 met inclusion/exclusion criteria. No studies examining the impact of nocturnal hemodialysis on mortality were identified. All studies reported improved blood pressure control after conversion to nocturnal hemodialysis. Data regarding the other health outcomes of interest revealed mixed results.

*Conclusion.* Nocturnal hemodialysis is a potential alternative to conventional intermittent hemodialysis. Before significant resources are invested in initiating nocturnal hemodialysis programs, further data on mortality and cardiovascular morbidity, preferably from randomized clinical trials, are required.

The first report of daily dialysis was in 1969 by DePalma et al, who described outcomes in 7 patients receiving dialysis 5 times per week, 4 to 5 hours per session [1]. These patients were selected for daily therapy mostly based on severe intradialytic hypotension; this problem resolved, and all patients reported improved appetite, weight gain, and general well-being. Other groups experimented with daily dialysis in the 1970s, and although clinical outcomes in selected patients appeared favorable, these programs were abandoned due to funding difficulties and the resource intensity of the treatment [2, 3].

The use of slow daily nocturnal hemodialysis (NHD) was revolutionized by a group in Toronto led by Robert Uldall and Andreas Pierratos. This program, initiated in 1994, has reported impressive results for selected patients who were treated with long, slow, overnight hemodialysis at home [4]. Subsequently, enthusiasm for NHD has been growing among renal programs in North America and Europe. In fact, many centers are examining the feasibility and attempting to obtain funding so that NHD can be routinely offered to patients requiring dialysis. This enthusiasm must be tempered by lack of randomized trials investigating the impact of NHD on clinical outcomes. In fact, existing studies on NHD have been small, have been done in highly select ESRD patients, and often present conflicting results. Given the substantial resources that would be required to initiate and maintain a NHD program, a critical evaluation of the available evidence is necessary to determine its potential role in the treatment of end-stage renal disease.

We performed a qualitative systematic review to gather and summarize all current evidence available on the effect of nocturnal dialysis on several key health parameters, including: (*1*) left ventricular hypertrophy and blood pressure control; (*2*) anemia; (*3*) calcium-phosphate balance; and (*4*) health-related quality of life (HRQOL). The study hypothesis was that nocturnal hemodialysis, in comparison to conventional hemodialysis, would have no impact on these key health parameters.

**Key words:** nocturnal hemodialysis, dialysis, systematic review.

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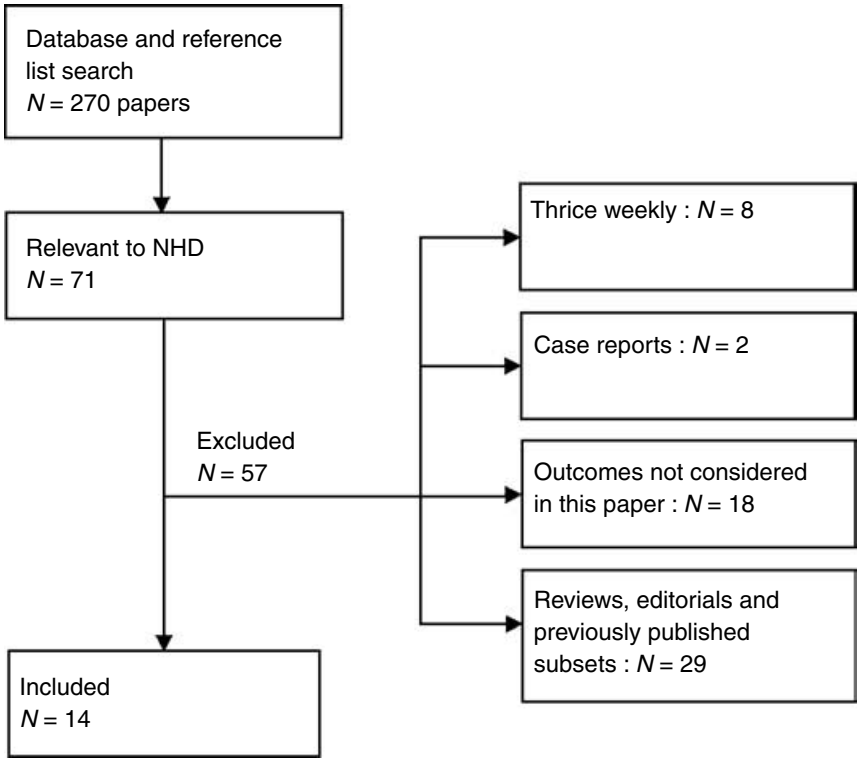


**Fig. 1. Flow diagram documenting inclusion and exclusion of nocturnal hemodialysis studies.**

## Review methods

A thorough review of available literature was undertaken. Inclusive databases were identified and included: Medline via Ovid (1966 to week 4 of July 2003), Embase via Ovid (1980 to week 4 of July 2003), Cochrane databases via Ovid, BioAbstracts via Silverplatter, Cinahl via Ovid, DARE via Ovid, Health Technology Assessment Database via York University, and Proceedings First via USC website. The search terms selected were "nocturnal" or "nightly" as keywords in titles or abstracts, and "dialysis," "hemodialysis" or "renal dialysis" as MESH or keywords. Non-English studies were included. Determination of search inclusiveness was judged by comparing the search results to recently published reviews. Additional studies were identified by review of reference lists, as well as communication with experts in the field. All abstracts were then manually reviewed by 2 independent reviewers (M.W. and B.M.) for relevancy to the study topic. Papers were included if they dealt with nocturnal hemodialysis (as defined by dialysis occurring at least 5 nights per week and at least 6 hours per night), reported on 1 of the 4 predefined outcomes of interest, and reported data in a quantitative fashion. Case reports (including studies with fewer than 5 patients), editorials, and review papers were excluded, as were short-term studies (i.e., less than 4 weeks) or studies that did not include a comparator group (i.e., case controls or pre-post within patient comparison). Multiple publications on single data sets were noted, and only the most recent papers were included, provided prior publications did not contain novel data. Efforts were made to contact authors of papers when concern about duplicate publication existed. Disagreements between reviewers were settled by a third reviewer (B.C.), and the remaining relevant papers were collected. Data on the 4 primary dialysis-related morbidities were manually extracted into a database with accompanying study design data, and were then distilled into individual tables for each of the selected outcomes studied. Due to the observational nature of the included studies, meta-analysis was not performed.

## Details of the included and excluded studies

The initial literature search returned 270 papers and abstracts (Fig. 1), 71 of which were found to be relevant to nocturnal dialysis. Of these, 7 papers and 1 abstract were based on thrice weekly NHD [5–11], 2 papers were case reports [12, 13], 16 papers and 2 abstracts did not report information on the clinical end points of interest [14–29], and 29 were either reviews, editorials, solely qualitative in nature, or contained previously published subsets of data [30–58]. The remaining 10 papers and 4 abstracts were included in the systematic review [59–68, abstracts; Brissenden J et al, *J Am Soc Nephrol* 9:168A, 1998; Chan C et al, *J Am Soc Nephrol* 13:60A, 2002; Chan C et al, *J Am Soc Nephrol* 14:498A, 2003; Lorch J, Pollak V, *J Am Soc Nephrol* 14:232A, 2003], although only part of the data (i.e., that dealing with longer-term outcomes of

**Table 1.** Study design of included papers

| Author | Study design | Study duration | Population | Treatment group | Comparison/ control group |
|---|---|---|---|---|---|
| Musci [65] | Prospective pre/post | 6 months | 7 IHD patients switched to NHD | 8 to 10 hours of nocturnal 6 to 7×/week | Baseline measurement prior to starting NHD |
| Brissenden J et al, *J Am Soc Nephrol* 9:168A, 1998 | Prospective pre/post (abstract) | 3 months | 18 IHD patients switched to NHD | 8 hours of nocturnal 6×/week | Baseline measurement prior to starting NHD |
| Lockridge [63] | Prospective pre/post | 6 months | 5 IHD patients switched to NHD | 7–9 hours of nocturnal 6×/week | Baseline measurement prior to starting NHD |
| McPhatter [64] | Prospective pre/post | 18 months | 11 patients switched from PD or IHD to NHD | 8 hours of nocturnal 6×/week | Baseline measurements prior to starting NHD |
| Williams [68] | Prospective pre/post | 6 to 8 weeks | 5 nondiabetic IHD patients switched to NHD (3 followed >4 weeks) | 8 hours of nocturnal 6×/week | Baseline measurements prior to starting NHD |
| Chan [59] | Prospective pre/post | Average 3.2 ± 2.1 years | 6 stable IHD patients with reduced ejection fraction switched to NHD | 8–10 hours of nocturnal 6×/week | Baseline measurement during 4 weeks prior to starting NHD |
| Chan [60] | Prospective nonrandomized pre/post with IHD control | Average 3.4 years for NHD and 2.8 years for IHD controls | 28 patients converted from IHD to NHD; 13 IHD controls | 8–10 hours of nocturnal 6×/week | Baseline measurements prior to starting NHD; 13 IHD controls |
| Chan C et al, *J Am Soc Nephrol* 13:60A, 2002 | Prospective pre/post (abstract) | 2 months | 15 patients converted from IHD to NHD | 8 hours of nocturnal 6×/week | Baseline measurements prior to starting NHD |
| Chan C et al, *J Am Soc Nephrol* 14:498A, 2003 | Retrospective cohort study (abstract) | 12 months | 63 patients converted from IHD to NHD; 31 IHD controls | 6–8 hours of nocturnal 5–6×/week | Baseline measurements prior to starting NHD; 31 IHD controls |
| London Quotidian HD Group | Prospective pre/post with case control | | 12 patients converted from IHD to NHD; 22 IHD controls (except Nesrallah—13 IHD to NHD and 19 matched IHD controls) | 8 hours of nocturnal 6×/week | Baseline measurements prior to starting NHD; 22 IHD controls |
| Lindsay [62] | Calcium-phosphate | Up to 30 months | | | |
| Heidenheim [61] | Quality of life | Up to 18 months | | | |
| Nesrallah [66] | Blood pressure | Up to 18 months | | | |
| Rao [67] | Anemia | Up to 18 months | | | |
| Lorch J, Pollak V, *J Am Soc Nephrol* 14:232A, 2003 | Prospective pre/post (abstract) | 2–23 months | 5 patients converted from IHD to NHD | Mean 4.8×/week | Baseline measurement prior to starting NHD |

NHD) was considered from 1 study [65]. Three of these papers presented data only in a semiquantitative form [63, 68, abstract; Lorch J, Pollak V, *J Am Soc Nephrol* 232A, 2003]. These data were included in the body of the text below, but were not summarized within the tables. For a complete list of abstracts that were excluded, please contact the corresponding author.

## RESULTS

### Relevant papers

Fourteen reports (Table 1) concerning the key outcome measures were identified. These comprised work from the groups in London (Canada), Toronto (Canada), Lynchburg (VA, USA), and Rochester (MN, USA). All identified studies were either pre-post within-patient comparison or case control studies. Average follow-up times ranged from 6 weeks to 3.4 years. Study sample sizes ranged from 5 to 63 NHD patients. There were large differences in reporting styles for any given clinical parameter. There were no randomized trials identified. No comparative data on survival or the occurrence of cardiac events were found. Two studies included a short daily dialysis comparator group in addition to the conventional and nocturnal groups [23, 68]. In these instances, data from patients receiving short daily dialysis were excluded.

### Blood pressure control and left ventricular hypertrophy

Four studies were identified in which blood pressure control parameters were the primary or secondary outcome measures (Table 2) [59, 60, 66, abstract; Chan C et al, *J Am Soc Nephrol* 13:60A, 2002]. Of these, 3 papers came from the Toronto group [59, 60, abstract; Chan C

**Table 2.** Impact of NHD on blood pressure and left ventricular hypertrophy

| Author | Blood pressure *mm Hg* | Antihypertensive use | LV mass index |
|---|---|---|---|
| Chan [59] | SBP 138 ± 10 to 120 ± 9 ($P$ 0.04)<br>DBP 80 ± 9 to 69 ± 7 ($P > 0.05$)<br>MAP 99 ± 6 to 86 ± 7 ($P$ 0.01) | 2.2 to 0.7 cardiovascular medications ($P$ 0.02) | 180 ± 54 g/m$^2$ to 143 ± 45 ($P > 0.05$) |
| Chan [60] | SBP 146 ± 20 to 122 ± 13 for NHD ($P < 0.001$ within NHD patients)<br>DBP 84 ± 15 to 74 ± 12 ($P < 0.05$ within NHD patients)<br>MAP 104 ± 16 to 90 ± 11 ($P < 0.05$ within NHD patients<br>No difference for comparison of NHD and IHD controls | 1.8 to 0.3 medications for NHD ($P < 0.001$ within NHD patients)<br>1.5 to 1.5 medications for IHD ($P > 0.05$ for comparison of NHD and IHD controls) | 147 ± 42 g/m$^2$ to 114 ± 40 g/m$^2$ for NHD ($P$ 0.004 within NHD patients)<br>142 ± 33 g/m$^2$ to 150 ± 56 for IHD ($P < 0.05$ for comparison of NHD and IHD controls) |
| Chan C et al, *J Am Soc Nephrol* 13:60A, 2002 | 24 hour SBP 134 ± 17 to 120 ± 8 ($P < 0.05$)<br>24 hour DBP 85 ± 11 to 75 ± 9 ($P < 0.05$) | 2.4 to 0.1 medications ($P < 0.05$) | Not reported |
| Nesrallah [66] | NHD MAP 117.1 ± 22.6 to 97.1 ± 8.4 ($P < 0.03$)<br>Control MAP 105.8 ± 12.8 to 104.5 ± 9.4 | NHD 3.3-fold reduction in tablets per day, 8/13 decreased or discontinued medications, decrease in dose-weighted score 0.202 ($P < 0.05$)<br>Control 1.4-fold increase in tablets per day, 1/10 decreased or discontinued medications | Not reported |

et al, *J Am Soc Nephrol* 13:60A, 2002]. Personal communication with the first author verified that data in each paper was novel. All studies used a case control or pre-post design. Nessrallah et al [66] measured blood pressure in the predialysis period, Chan et al [59] took measurements at clinic visits, and a later study by the same group used 24-hour ambulatory blood pressure measurements [abstract; Chan C et al, *J Am Soc Nephrol* 13:60A, 2002]. Another report did not specify when blood pressure measurements were obtained [60]. Three papers report systolic blood pressures, and all of them reported a significant reduction in systolic blood pressure by the end of the study period in the NHD [59, 60, abstract; Chan C et al, *J Am Soc Nephrol* 13:60A, 2002]. Diastolic blood pressure was reported in 3 studies, revealing a significant reduction in 2 studies [60, abstract; Chan C et al, *J Am Soc Nephrol* 13:60A, 2002] in NHD patients, and a trend toward reduction in the third [59]. Two studies reported mean arterial blood pressure (MAP), and this was reported to be significantly lower in the NHD group [60, 66]. These same 2 reports included a comparison to matched IHD controls. Neither of these found a significant difference in blood pressure between the NHD and IHD patient groups.

Antihypertensive medication use was significantly reduced following institution of NHD in all studies in the nocturnal group [59, 60, 66, abstract; Chan C et al, *J Am Soc Nephrol* 13:60A, 2002]. Extracellular fluid volume did not appear to change between conventional and nocturnal groups in the 3 studies in which it was reported [59, 60, 66].

Three other papers reported on blood pressure in 5 NHD patients although the data were only reported in a semiquantitative fashion. Williams et al [68] reported blood pressure control was achieved with fewer antihypertensives and a trend toward reduction in predialysis MAP by the end of 8 weeks on NHD for 4 patients. Lorch and Pollak [abstract; Lorch J, Pollak V, *J Am Soc Nephrol* 14:232A, 2003] reported improved blood pressure control in 2 of 5 patients converted to NHD, and Lockridge et al [63] showed improved blood pressure control with fewer medications in 4 out of 5 patients.

Left ventricular hypertrophy was assessed as a primary outcome in 2 papers (Table 2) [59, 60]. One study, in NHD patients without congestive heart failure, showed a significant reduction in LV mass after 12 months of NHD; LV mass was also reduced compared to a matched IHD population [60]. The other study, in patients with congestive heart failure, showed a nonsignificant reduction in LV mass, and a significant improvement in ejection fraction following conversion to NHD [59].

## Anemia

Three studies were identified that reported changes in hemoglobin as an outcome (Table 3) [59, 67, abstract; Chan C et al, *J Am Soc Nephrol* 14:498A, 2003]. All 3 studies noted a significant increase in hemoglobin for patients after conversion to NHD. However, there was no significant difference noted between the IHD control group and the NHD group in Rao et al [67]. Another paper by Chan et al [60], which included a subset of patients from a later publication, also reported no difference in hemoglobin when comparing the NHD group to a matched IHD control group. However, this same study noted a significant increase in hemoglobin in the NHD patients after conversion from conventional to nocturnal hemodialysis.

**Table 3.** Impact of NHD on hemoglobin and erythropoietin use

| Author | Hemoglobin *g/dL* | Erythropoietin dose |
|---|---|---|
| Chan [59] | 11.6 ± 1.0 to 13.1 ± 1.4 ($P = 0.05$) | Not reported |
| Chan C et al, *J Am Soc Nephrol* 14:498A, 2003 | IHD: 11.0 ± 0.2 to 11.5 ± 0.2 (12 mos), ($P > 0.05$)<br>NHD: 11.5 ± 0.2 to 12.3 ± 0.2 g/L (12 mos) ($P = 0.03$) | IHD: 8258 ± 1166 to 8607 ± 1087 u/wk (12 mos) ($P > 0.05$)<br>NHD: 10405 ± 1388 to 7652 ± 1107 u/wk (12 mos) ($P = 0.03$) |
| Rao [67] | IHD: 11.79 ± 1.92 to 11.49 ± 0.74<br>NHD: 10.95 ± 1.79 to 11.94 ± 1.66 ($P < 0.05$ within NHD patients; $P > 0.05$ for comparison of NHD and IHD controls) | IHD 0.79 ± 0.78 U/wk/kg/g/L to 0.63 ± 0.45<br>NHD 1.36 ± 1.49 U/wk/kg/g/L to 1.76 ± 1.78 ($P > 0.05$ within NHD patients and for comparison of NHD and IHD controls) |

**Table 4.** Impact of NHD on mineral metabolism

| Author | PTH | Calcium | Phosphate | $Ca \times PO_4$ | Meds |
|---|---|---|---|---|---|
| Musci [65] | 49.7 ± 26.7 pmol/L to 19.0 ± 23.9 (not statistically different) | 9.6 ± 0.8 to 9.6 ± 1.0 mg/dL (not statistically different) | Serum $PO_4$ control: 6.50 ± 1.55 mg/dL<br>Serum $PO_4$ NHD: 4.02 ± 0.62 mg/dL ($P < 0.01$) | Not reported | Calcium carbonate: 2400 (1400 to 4500) mg/d to 0 (0 to 1500) mg/d ($P < 0.05$) |
| Chan [60] | IHD: 40.7 ± 36.2 pmol/L to 40.1 ± 30.0<br>NHD: 34.9 ± 55.0 to 16.6 ± 24.3<br>($P > 0.05$ within NHD patients and for comparison of NHD and IHD controls) | Not reported | Not reported | Not reported | Not reported |
| Lindsay [62] | IHD: 286.7 ± 252.5 pg/mL to 76.5 ± 8.7<br>NHD: 235.3 ± 262.7 pg/mL to 171.9 ± 173.2<br>($P > 0.05$ within NHD patients and for comparison of NHD and IHD controls) | IHD: 9.9 ± 0.8 mg/dL to 9.9 ± 1.0<br>NHD: 10.1 ± 1.0 mg/dL to 10.2 ± 0.1<br>($P > 0.05$ within NHD patients and for comparison of NHD and IHD controls) | Predialysis IHD: 5.7 ± 1.7 mg/dL to 5.3 ± 1.3<br>Predialysis NHD: 5.0 ± 1.5 mg/dL to 3.9 ± 1.1<br>($P > 0.05$ for all within NHD patients and between group comparisons) | IHD: 57.3 ± 18.9 mg2/dL2 to 52.5 ± 12<br>NHD: 50.6 ± 14.9 mg2/dL2 to 38.1 ± 11.5<br>($P < 0.05$ for comparison of NHD and IHD controls; $P > 0.05$ within NHD patients) | Calcium carbonate phosphate binder dose<br>IHD: 2823 ± 1099 mg/d to 3101 ± 2872 mg/d<br>NHD: 2589 ± 2157 mg/d to 900 ± 1273<br>($P > 0.05$ for within NHD patients and between group comparisons) |

Two papers also examined the impact of NHD on erythropoietin dose (Table 3) [67, abstract; Chan C et al, *J Am Soc Nephrol* 14:498A, 2003]. Chan et al noted a significant reduction in weekly dose after conversion to NHD, with no change in the IHD control group's dose. The second study found no significant reduction in dose after conversion to NHD, although there was a trend toward reduction [67]. In both studies, the IHD control group started with a lower average weekly erythropoietin dose. Additionally, Lockridge et al [63] reported that the hemoglobin of 4 out of 5 patients could be maintained on lower doses of erythropoietin.

### Calcium-phosphate metabolism

Three studies were identified that examined the effects of NHD on calcium and phosphate balance (Table 4) [60, 62, 65]. None of these studies noted a significant difference in serum PTH after conversion to NHD, and of the 2 studies that had IHD control groups, neither study noted a significant difference in serum PTH between groups. In the 2 papers reporting serum calcium data, no significant difference was noted after conversion to NHD [62, 65]. Two studies examined the effect of NHD on serum phosphate. One study noted a significant reduction in serum phosphate after 6 months of NHD [65]. The second study noted no significant reduction in serum phosphate after 30 months of NHD, and noted no differences between NHD patients and IHD controls with respect to serum phosphate [62]. In the 2 studies that examined the impact of NHD on phosphate binding medications, only 1 study noted a significant reduction in calcium carbonate [65]. The remaining study found a nonsignificant trend toward reduction in phosphate binding medications in the NHD group [62]. The study by Williams et al showed a significant decrease in mean phosphate ($P = 0.04$) and an increase in serum calcium ($P = 0.031$), while PTH showed a trend toward reduction that was nonsignificant [68]. Lockridge et al [63] also showed that phosphate binders could be discontinued in all patients within 3 months of starting NHD, and most required phosphate supplementation in dialysate to maintain a normal serum phosphate level. In the London study, calcium phosphate product

was reported; a significant reduction was noted for the NHD patients compared with the IHD control group [62]. However, no significant difference was observed between the initiation of NHD and the end of the study.

### Health-related quality of life

Studies that reported health-related quality of life outcomes had no common reporting method, and full details of the quality-of-life assessment tools/scores were not available in any study [61, 63, 64, abstract; Brissenden J et al, *J Am Soc Nephrol* 9:168A, 1998]. Brissenden examined the effect of NHD on Sickness Impact Profile (SIP; composed of 12 subscales with lower scores indicating improvement) [69] and SF-36 scores (composed of 8 subscales from 0 to 100 with higher scores indicating improvement) [70]. Only subscale scores for which a statistically significant improvement or trend toward improvement were reported. The SIP showed an improvement in the total score (14 to 9.5; $P = 0.03$), eating (14.2 to 3.7; $P = 0.003$), and household management (25.6 to 15; $P = 0.01$). Trend to improvement was seen in ambulation (17.2 to 11.1; $P = 0.07$), mobility (3.9 to 2.9; $P = 0.08$), and social interaction (16.4 to 11.4; $P = 0.07$). The SF-36 showed improvements in social functioning (54.2 to 79.2; $P = 0.006$), physical functioning (60.6 to 69; $P = 0.008$), and role-physical (39.2 to 36.1; $P = 0.05$). General health (39.6 to 46.0; $P = 0.14$) and vitality (46.4 to 56.5; $P = 0.13$) showed a trend to improvement. An improvement (8.5 to 6.0; $P = 0.02$) was also noted in the Beck Depression Inventory score. McPhatter et al [64] published the SF-36 portion of the CHOICE questionnaire results applied preinitiation of NHD and 3 and 6 months' postinitiation. The CHOICE questionnaire is an ESRD-specific health-related quality-of-life assessment tool composed of 21 domains containing 83 items. Higher scores indicate a better quality of life than lower scores. *P* values were not reported, but improvements were noted in 5 patients: physical functioning 59 to 85, pain index 45 to 85, vitality 40 to 75, role-emotion 45 to 94, social functioning 46 to 87, health perceptions 47 to 70, and role-physical 31 to 85. Scores were not improved in the mental health domain of the SF-36 component of the CHOICE questionnaire. Heidenheim et al [61] published the results of the London group, which used the Renal Disease Specific Quality of Life indicators, SF-36, and time trade-off scores. An initial improvement (at month 9) in the Renal Disease Specific Quality of Life indicators was noted after conversion to nocturnal hemodialysis, although no difference was noted 18 months after conversion to NHD, or when NHD patients were compared to the IHD control group. Moreover, the physical and mental composite scores of the SF-36 did not change after conversion to NHD, or when compared to the IHD control group. When the time trade-off method, which represents a single global measure of HRQOL, was used, the NHD group improved from $0.23 \pm 0.24$ to $0.78 \pm 0.17$ ($P < 0.05$). However, when time trade-off scores were compared between NHD patients ($0.78 \pm 0.17$) and the matched IHD comparison group ($0.70 \pm 0.27$), no difference was noted. Lockridge et al [63] reported data on 5 patients at 6 months after starting NHD, showing a greater than 45% improvement in 7 domains of the SF-36, and in 6 of these, at least an 85% improvement.

## DISCUSSION

To our knowledge, this represents the first systematic review of health-related outcomes in nocturnal hemodialysis. An inclusive search strategy was employed to enable potential capture of nonpublished data, as well as studies published in well-known nephrology journals. While individual studies have generally been supportive of NHD over IHD, the magnitude of improvement in specific parameters has varied markedly between studies.

The current literature suggests a benefit of NHD in several areas. There is general agreement that systolic, mean arterial, and diastolic pressure are improved after conversion to NHD, and that fewer antihypertensives are required to achieve this control. Interpretation of this data, however, is complicated by a lack of difference between NHD patients after conversion and their IHD controls [60, 66]. With regard to the regression of LVH, results are similarly mixed, even within a single center's experience [59, 60].

Regarding the impact of NHD on anemia, a consistent improvement in hemoglobin is seen after conversion to NHD, although no difference has been noted when compared to IHD controls [59, 67, abstract; Chan C et al, *J Am Soc Nephrol* 14:498A, 2003]. Interpreting this data is difficult as only Rao et al [67] reported a target hemoglobin level. Without a prespecified target, improvements in hemoglobin control may simply reflect improved vigilance in the NHD group. Complicating this data even further is the inequality of hemoglobin levels at baseline. As seen in Rao et al [67], the IHD control group trended toward a higher baseline hemoglobin level and lower baseline mean erythropoietin dose than the NHD group. The decrease in erythropoietin use after conversion to NHD also remains to be clarified with only one study reporting a significant reduction in dose [abstract; Chan C et al, *J Am Soc Nephrol* 14:498A, 2003].

In the area of mineral metabolism there is no clear consensus on the impact of NHD on serum calcium, phosphate, or PTH, although some studies reported a significant reduction in the use of phosphate-binding medications. The interpretation of these results is complicated given the frequent need to liberalize phosphate intake, and the addition to phosphate to the dialysate of some patients treated with NHD. Unfortunately, most studies

did not quantify phosphate intake, and dietary journals were not reported.

Health-related quality-of-life measures appear to improve after conversion to NHD, although the degree and clinical significance of improvements in quality of life have been variable. For example, some small studies reported a greater than 85% improvement in selected domains of quality of life, while others noted only minimal improvement [63, 64].

One of the strengths of this study is that we followed contemporary guidelines for the conduct and reporting of meta-analyses of observational studies [71]. The strength of our conclusions, however, is limited by the existing literature. We were unable to find any data on hard clinical outcomes associated with NHD, including survival and cardiovascular end points. The numbers of patients in all studies was quite limited, reducing their statistical power. In addition, differences in the reporting styles for some outcomes make direct comparison of studies difficult. Finally, the specific mechanisms through which NHD may actually improve health outcomes also remain uncertain.

Several potential limitations of this study should be considered. First, for the outcomes considered, there is little potential for summary analyses, given the nature of the data. Second, as the health outcomes investigated were chosen a priori to the literature review, several clinically important outcomes were not reviewed, including nutrition, sleep-related disorders, dialysis adequacy, and access complications. It is important to note that the lack of standardization in reporting on these variables makes comparing their outcomes difficult. Third, in the time subsequent to the search for papers to be included in this review, more data have become available regarding NHD. This is an inherent limitation of systematic reviews. For example, subsequent to our search strategy, Chan et al have published results of a mechanistic analysis performed to elucidate the biology underlying the blood pressure reduction seen in NHD [72], and McFarlane et al have published the results of a quality-of-life assessment in NHD [73].

Because of the adverse patient outcomes associated with conventional hemodialysis, it is understandable that NHD has been greeted with enthusiasm by nephrologists. However, no published trial of NHD has used a randomized design, and observational studies have well-known limitations. Although randomized trials are relatively infrequent in dialysis populations [74, 75], we believe that such a study is required before NHD can be widely recommended, especially given the substantial cost and time associated with the initiation of an NHD program. Although a randomized study that was powered for a clinically relevant difference in mortality would probably require thousands of patients, our data suggest that markedly fewer subjects would be required to properly evaluate the effect of NHD on continuous outcomes. For example, to detect a 20% reduction in magnetic resonance measured left ventricular mass due to NHD (similar to the effect size reported by Chan et al [60]), a randomized study would achieve 90% power with 18 subjects per arm, assuming no change in subjects receiving conventional hemodialysis and a 15% drop-out rate due to transplantation. While it could be argued that a randomized trial of NHD would pose ethical issues, given that it is increasingly being offered as routine therapy, we believe that this highlights the need to conduct such a study so that NHD is not established as the standard of care without appropriate evaluation.

## CONCLUSION

NHD is a potential alternative to conventional thrice-weekly hemodialysis. The fundamental concept of a more "physiologic" dialysis has appeal, and today's dialysis technology is making this approach more feasible. However, current data are incomplete and have potentially serious methodologic limitations. Given the potential bias noted within existing research, a randomized clinical trial comparing nocturnal hemodialysis to conventional thrice-weekly hemodialysis is needed.

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