Daily Hemodialysis: A Systematic Review

Rita S. Suri,* Gihad E. Nesrallah,† Rahul Mainra,* Amit X. Garg,*‡ Robert M. Lindsay,* Tom Greene,§ and John T. Daugirdas‖

*Division of Nephrology and †Department of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario, and ‡Division of Nephrology, Humber Regional Hospital, Toronto, Ontario, Canada; §Department of Quantitative Health Sciences, Cleveland Clinic Research Foundation, Cleveland, Ohio; and ‖Department of Medicine, University of Illinois, Chicago, Illinois

Several studies have reported improved outcomes with daily hemodialysis (DHD), but the strength of this evidence has not been evaluated. The published evidence on DHD was synthesized and its quality rated to inform need and sample size calculations for a randomized trial. Citations were identified in MEDLINE and EMBASE using validated search strategies. Dialysis journals that were not indexed and bibliographies of relevant articles were hand-searched. Two authors reviewed all citations. Articles that reported original data on five or more adults who were receiving DHD (1.5 to 3 h, 5 to 7 d/wk) for ≥3 mo were included. Twenty-five articles reporting 14 unique populations with 268 patients (five to 72 per study) met inclusion criteria. Of the 14 cohorts, 13 were studied with an observational design, 10 were studied prospectively, and four had parallel control groups. Mean age ranged form 41 to 64 yr, mean time on dialysis was 2 to 11 yr, 0 to 28% of patients had diabetes, >90% had arteriovenous fistulae, and >50% were dialyzed at home. Most data were described at ≤12 mo of follow-up. Outcomes included quality of life, cardiovascular disease, erythropoiesis, nutritional status, hospitalizations, and vascular access failures. Reporting was too heterogeneous to allow pooling of data. Ten of 11 studies suggested improvements in blood pressure; findings for other outcomes varied. Discontinuation of DHD occurred in 0 to 57% in-center and 0 to 15% home patients. Studies of DHD are limited by small sample size, nonideal control groups, selection and dropout biases, and paucity of data on potential risks. Randomized trials with adequate statistical power are required to establish the efficacy and the safety of DHD.


Interest in frequent hemodialysis (HD) regimens has grown substantially during the past decade. Delivered as either daily (1.5 to 2.5 h, 6 d/wk) or nocturnal (6 to 8 h, 6 d/wk) treatments, frequent HD has been reported to result in improved outcomes compared with conventional HD in several observational studies. On the basis of these studies, proponents of frequent HD have been lobbying governments in North America and elsewhere to fund these therapies as treatment options for patients with ESRD, whereas others have advocated that a randomized, controlled trial that definitively evaluates outcomes with frequent HD is needed before its widespread acceptance. Adopting techniques described by Stroup et al. (1), we conducted a systematic review to synthesize and rate the quality of current evidence with respect to the potential benefits and risks of daily HD (DHD) to inform need and sample size calculations for a randomized trial.

Materials and Methods

Research Questions

The primary questions of this review were as follows: (1) What is the published experience with DHD? (2) What is the methodologic quality of these studies? (3) What is the magnitude of benefits and risks of DHD reported in these studies?

Included Studies

Published full-text case series, cohort studies, and randomized, controlled trials were included when two investigators independently agreed that the article described original data for a population of five or more adults (≥18 yr of age), who were receiving DHD (defined as 1.5 to 3 h/session, 5 to 7 d/wk), and reported a follow-up time of ≥3 mo. The location of daily dialysis could be either at home or in-center. For studies that seemed to describe the same cohort of patients, the most recent study with the most complete data was included. Articles that reported cost-effectiveness and met the above criteria were included, provided that they had original outcome data (e.g., utility measures); articles that report only absolute costs without outcomes were excluded. Abstracts were excluded because of difficulties with accurate data abstraction. A third investigator resolved disagreements with respect to study inclusion.

Finding Relevant Studies

An independent review of citations from MEDLINE (OVID 1966 to May 31, 2005) and EMBASE (OVID 1980 to May 31, 2005) bibliographic databases was conducted by two investigators. Full-text articles were bits would be: (1) What is the published experience with DHD? (2) What is the methodologic quality of these studies? (3) What is the magnitude of benefits and risks of DHD reported in these studies?

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Methodologic Assessment

To summarize succinctly the design characteristics of the included studies, two investigators (R.S. and G.N.) developed a methodologic assessment tool, on the basis of criteria of internal and external validity suggested for studies of therapy (2) (Table 1). Each article was rated independently using this tool, and disagreements were resolved by consensus.

Data Abstraction

Using standardized forms, two reviewers (R.S. and R.M.) extracted data on study, patient, and treatment characteristics, as well as on patient outcomes and potential risks of DHD. Outcomes were divided into the following categories: (1) Health-related quality of life and related parameters, (2) cardiovascular disease, (3) erythropoiesis, (4) nutrition, (5) mineral metabolism and bone disease, and (6) hospitalizations. A description of the validated questionnaires that were used to assess health-related quality of life is given in Appendix 1. Risks that were evaluated were vascular access failures, blood loss, and nonadherence to therapy. When results were presented at multiple follow-up times within the same article, data that were reported at the longest follow-up time was extracted. All disagreements were resolved by a third reviewer (G.N.).

Results

Finding and Selecting Studies

More than 800 citations in six languages were screened from all sources, and 233 full-text articles were retrieved for detailed review. Twenty-nine articles met inclusion criteria (3–31). The agreement beyond chance between two independent reviewers for article inclusion was excellent ($\kappa = 0.86$).

Reasons for excluding citations were as follows: Abstracts (13 citations), patients not on DHD (72 citations), children (one citation), fewer than five patients (four citations), follow-up <3 mo (three articles), review articles or editorials without original data (46 citations), kinetic modeling theories (31 citations), and economic articles that reported costs without outcomes (three citations). Two authors independently excluded two articles because they did not examine clinical outcomes. An additional 29 articles reported similar outcomes for the same cohorts of patients as the 29 included articles but at earlier follow-up.

Table 1. Methodologic assessment of included articles

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Cohorts that Met Criterion</th>
<th>$n/N$</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the study a randomized, controlled trial?</td>
<td>1/14</td>
<td>1/14</td>
<td>7</td>
</tr>
<tr>
<td>For randomized trials, was the allocation described and concealed?</td>
<td>0/1</td>
<td>0/1</td>
<td>0</td>
</tr>
<tr>
<td>If not a randomized, controlled trial, then was there a separate control group?</td>
<td>3/13</td>
<td>3/13</td>
<td>23</td>
</tr>
<tr>
<td>Were participant inclusion and exclusion criteria described clearly?</td>
<td>9/14</td>
<td>9/14</td>
<td>64</td>
</tr>
<tr>
<td>Was there a clear description of participants’ demographic and prognostic factors at baseline?</td>
<td>12/14</td>
<td>12/14</td>
<td>86</td>
</tr>
<tr>
<td>Were the treatment and control groups similar with respect to prognostic factors at baseline?</td>
<td>2/4</td>
<td>2/4</td>
<td>50</td>
</tr>
<tr>
<td>Was the intervention (i.e., the delivered dialysis prescription) clearly described?</td>
<td>6/14</td>
<td>6/14</td>
<td>43</td>
</tr>
<tr>
<td>Were participants in both study groups treated equally with respect to co-interventions?</td>
<td>2/4</td>
<td>2/4</td>
<td>50</td>
</tr>
<tr>
<td>Were the methods used to measure outcome parameters clearly described?</td>
<td>12/14</td>
<td>12/14</td>
<td>86</td>
</tr>
<tr>
<td>Was the assessment of outcomes similar in both study groups? (For studies without control groups, was the assessment of outcomes similar at baseline and at follow-up?)</td>
<td>13/13</td>
<td>13/13</td>
<td>100</td>
</tr>
<tr>
<td>Were the assessors of any subjective outcomes blinded to participants’ treatment allocation?</td>
<td>0/4</td>
<td>0/4</td>
<td>0</td>
</tr>
<tr>
<td>Were the participants’ outcomes analyzed in the group to which they were allocated (intent-to-treat analysis)?</td>
<td>3/4</td>
<td>3/4</td>
<td>75</td>
</tr>
<tr>
<td>Were confidence intervals reported for most outcomes?</td>
<td>3/14</td>
<td>3/14</td>
<td>21</td>
</tr>
<tr>
<td>Was a prospective statistical power calculation performed and reported?</td>
<td>1/13</td>
<td>1/13</td>
<td>8</td>
</tr>
<tr>
<td>Were potential risks reported (e.g., vascular access failures)?</td>
<td>11/14</td>
<td>11/14</td>
<td>79</td>
</tr>
<tr>
<td>Was modality survival (i.e., the number of patients continuing daily HD at last follow-up) or adherence to therapy reported?</td>
<td>7/14</td>
<td>7/14</td>
<td>50</td>
</tr>
<tr>
<td>Was the loss to follow-up reported and &lt;10%?</td>
<td>10/14</td>
<td>10/14</td>
<td>71</td>
</tr>
</tbody>
</table>

*There were 25 included studies, but in some instances, multiple studies reported on a single cohort of patients who were undergoing daily hemodialysis (DHD). Thus, data are reported here as number of cohorts. The denominator indicates the total number of cohorts where it was applicable to evaluate the criterion.

This criterion is not applicable to one observational study for which outcomes were evaluated only at follow-up (15).
times (32–60). (References for excluded studies available on request.)

Of the 29 included articles, 25 were published in 1998 or later, and four were published before 1982. Dialysis practices over the last three decades have changed considerably, potentially reducing the current applicability of findings from these four earlier studies. Thus, these four studies are described only briefly in this review (3–6). Ultimately, 25 articles that described 14 cohorts of at least 268 unique patients were included for methodologic assessment and complete data abstraction (7–31).

Methodologic Assessment of Included Articles

Because several included studies described different outcomes for the same cohort of patients, the methodologic assessment was performed for each of the 14 unique cohorts (Table 1). Only one study used a randomized design; this was a randomized crossover trial (23). Of the 13 observational cohort studies, three reported enrolling separate control groups. No study reported that blinded adjudicators assessed subjective outcome measurements, such as manual blood pressure, left ventricular mass index by echocardiogram, dry body weight, utility scores, etc. The loss to follow-up was low in the majority of studies. No study met all methodologic criteria. The mean number of criteria met for all cohorts was 56% (range 11 to 71%); for cohorts with control groups, it was 66% (range 57 to 71%).

Patient and Treatment Characteristics

Table 2 summarizes the demographic and treatment characteristics of 17 cohorts of DHD patients reported in 29 studies during the period 1966 to 2004. The 14 cohorts reported in 1998 or later represent at least 268 unique patients from 21 centers in eight countries. The mean time on DHD ranged from 3 to 58 mo (7–31).

The majority of patients performed DHD at home. The HD prescription varied from 1.5 to 3 h, 5 to 7 d per week. However, the actual delivered treatment time and frequency were reported for six of 14 cohorts (8,14–16,24,31). Most studies did not report HD dose.

Patient preference as a result of lifestyle or other reasons seemed to be at least one reason for prescribing DHD in 12 of 14 cohorts. Six cohorts enrolled only patients who were “medically stable” or able to undergo home or out-of-hospital HD (7,15,21,24,27,31), whereas five cohorts also included patients with a specific medical indication for DHD, such as uncontrolled hypertension, intradialytic hypotension on conventional HD, malnutrition, etc. (14,16,17,19,24). One cohort was selected solely on the basis of medical indication (23), and indications were not specified for one cohort (22).

The mean age of patients ranged from 45 to 64 yr, and the majority of patients were male (range 33 to 100%). All except three cohorts were composed entirely of prevalent patients who had been on conventional HD for at least 6 mo; the mean time on conventional HD ranged form 2 to 11 yr. The percentage of patients with diabetes was 0 to 28%, and >90% of patients had arteriovenous fistulae or grafts.

Outcomes with DHD

Selected outcomes that were reported in individual studies are summarized in Table 3. Although the reported mean time on DHD ranged from 3 to 58 mo (Table 2), all studies reported continuous outcomes between 3 and 24 mo of follow-up, with the majority at 12 mo.

Outcome measures, units of measure, and length of follow-up were too heterogeneous to allow pooling of data from individual studies. For example, multiple instruments and methods were used to measure health-related quality of life and nutrition. BP measures were variable and included predialysis, office, and 24-h ambulatory BP. Reporting of erythropoietin dose was reported in absolute units in some studies, whereas it was normalized to body weight or hemoglobin in others.

Findings varied considerably between studies with respect to most outcomes (Table 3), but two findings were relatively consistent. Decreases in systolic or mean arterial BP were reported in 10 of 11 studies (10,14,16,17,22–24,27,29,31), whereas six of eight studies found no statistically significant change in phosphate or phosphate binder dose with DHD at 3 to 24 mo of follow-up (12,14,16,24,26,27). Health-related quality of life improved in some studies but not in others. Improvements were seen in hematocrit, hemoglobin, or erythropoietin dose in 7 of 11 studies (14,16,17,22,24,29,31). Albumin increased in 5 of 10 studies (11,16,18,22,29).

The single randomized trial reported similar findings as the observational studies (23). Twelve hypertensive conventional HD patients were randomly assigned in a crossover design to DHD and conventional HD, with each period lasting 6 mo. On DHD, the 24-h ambulatory blood pressure decreased by 20 mmHg (P < 0.01), while antihypertensive medication use was reduced. The left ventricular mass index decreased by 28 g/m² (P = 0.01). Extracellular water as measured by bioimpedance was reduced by 5.1% (P = 0.02). Estimates of variance were not provided. There was no observed change in hemoglobin, erythropoietin dose, or albumin.

No study was able to evaluate mortality, and only one study evaluated hospitalization rates and length of stay (14). Hospital admission rates and mean length of stay for up to 6 yr on DHD were compared with admission rates and length of stay for the entire cohort during their 12 mo before starting DHD. The hospitalization rate decreased from 2.5 ± 2.7 per patient year during the year on conventional HD before starting DHD to 1.5 ± 0.9 per patient year on DHD (mean follow-up 18.9 mo; P = 0.002). Similarly, the mean length of stay decreased from 12.2 ± 16.1 to 8.0 ± 58.5 d per patient year (P < 0.0001). However, 22 of the 42 patients in this cohort had died by 1 yr of follow-up, and only four of 42 remained by 6 yr (14).

Potential Risks of DHD

Potential risks of DHD include increased blood loss through the dialyzer and vascular access, as well as an increased risk for vascular access failure as a result of more frequent cannulation. The issue of blood loss was addressed in six cohorts. One study reported increased intravenous iron requirements with DHD (27). In another, the authors speculated that increased fre-
Table 2. Daily HD programs with five or more patients and ≥3 months of follow-up, 1966 to 2004

| Reference | Center | Study Design | Type of Study | Control Group | N | Dialysis Regimen | Home/In-Center | Weekly stdKt/V | Weekly spKt/V | Age (Yr) | Time on CHD (Yr) | % Prevalent | % Male | % Diabetes | Time on DHD (Mo) |
|-----------|--------|--------------|---------------|---------------|---|------------------|----------------|---------------|---------------|----------|----------------|-------------|--------|------------|----------------|-----------------|
| (3)       | Los Angeles, CA, USA | Pros. obs. | Parallel | 7 | 100% | 30 ± 0.3 | 5 to 6 | 20 ± 0.3 | 5 ± 1.0 | 45 ± 11 | 5.7 | 100 | 90 | 60 | 20 to 43 |
| (4)       | Bologna, Italy | Ret. obs. | Pre-post | 6 | Home | 2.9 ± 0.5 | 5 ± 0.5 | 60 ± 17 | 6.5 ± 0.9 | 100 | 60 | 6 | 100 | 60 | 100 | 20 to 43 |
| (5,6)     | Brooklyn, NY, USA | Pros. obs. | Pre-post | 10 | In-center | 2.2 ± 0.5 | 5 ± 0.5 | 7.7 ± 0.6 | 100 | 60 | 100 | 60 | 60 | 100 | 60 | 100 | 20 to 43 |
| (7–13)    | London, Ontario, Canada | Pros. obs. | Parallel | 11 | Home | 3.0 ± 0.3 | 5 to 6 | 45 ± 0.3 | 5 ± 1.0 | 100 | 60 | 60 | 100 | 60 | 100 | 20 to 43 |
| (14)      | Mountain View, CA, USA | Ret. obs. | Pre-post | 42b | Both | 2.7 ± 0.29 | 4.5 ± 0.8 | 46 ± 0.29 | 4.5 ± 0.8 | 100 | 60 | 60 | 100 | 60 | 100 | 20 to 43 |
| (15)      | Multicenter, USA | Pros. obs. | Pre-post | 23 | Both | 2.2 ± 0.5 | 5 ± 0.5 | 7 ± 0.6 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |
| (16)      | Multicenter, USA/Europe | Ret. obs. | Pre-post | 72 | Both | 15 ± 0.1 (1 to 30) | 5 to 6 | 45 ± 0.5 | 5 ± 1.1 | 100 | 60 | 60 | 100 | 60 | 100 | 20 to 43 |
| (17,18)   | Lyon, France | Pros. obs. | Pre-post | 36b | Both | 2.7 ± 0.29 | 4.5 ± 0.8 | 46 ± 0.29 | 4.5 ± 0.8 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |
| (19,20)   | Catanzaro, Italy | Ret. obs. | Pre-post | 22b | Both | 1.5 ± 0.5 | 5 ± 0.5 | 7 ± 0.6 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |
| (21)      | Perugia, Italy | Pros. obs. | Parallel | 24 | Both | 2.2 ± 0.5 | 5 ± 0.5 | 7 ± 0.6 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |
| (22)      | Perugia, Italy | Ret. obs. | Pre-post | 23 | Both | 1.5 ± 0.5 | 5 ± 0.5 | 7 ± 0.6 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |
| (23)      | Perugia, Italy | Cross-over RCT | Pre-post | 12 | Both | 1.5 ± 0.5 | 5 ± 0.5 | 7 ± 0.6 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |
| (24,25)   | Turin, Italy | Pros. obs. | Pre-post | 25–28 | Both | 2.0 ± 0.3 | 5 ± 0.6 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |
| (26,27)   | Utrecht, Netherlands | Pros. obs. | Parallel | 13 | Both | 4.1 ± 0.7 | 6 ± 0.6 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |
| (28)      | Brussels, Belgium | Ret. obs. | Pre-post | 9 | Both | 3.2 ± 0.2 | 5 ± 0.5 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |
| (29,30)   | Niteroi, Brazil | Pros. obs. | Pre-post | 5 | Both | 3.5 ± 0.5 | 6 ± 0.5 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |
| (31)      | Multicenter, Japan | Pros. obs. | Pre-post | 23 | Both | 4.1 ± 0.7 | 6 ± 0.6 | 100 | 60 | 60 | 100 | 60 | 60 | 20 to 43 |

NR, not reported; CHD, conventional hemodialysis; DHD, daily hemodialysis; Pros. obs., prospective observational; Ret. Obs., retrospective observational; RCT, randomized controlled trial; std, standard. When available, continuous data presented as mean ± SD, with ranges in parentheses (except OS presented as median ± SD).

aOn CHD for >6 mo.
bThese studies report continuous outcomes only for patients who completed at least 1 yr of DHD.
cGreater than 50% of patients in this study allowed to alternate DHD with 3 to 4x/wk.
Table 3. Summary of outcomes data from DHD programs with five or more patients and ≥3 months of follow-up, 1998 to 2004

<table>
<thead>
<tr>
<th>Category</th>
<th>Outcome</th>
<th>Positive Findings (P &lt; 0.05)</th>
<th>Nonsignificant Trends/No Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health-related quality of life</td>
<td>SF-36 PCS score</td>
<td>Increase by 9 points (17)</td>
<td>Increase (trend) (9)</td>
</tr>
<tr>
<td></td>
<td>SF-36 MCS score</td>
<td>Increase by 4 to 9 points (9,17)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>SF-36 subscales scores</td>
<td>—</td>
<td>No change in 6/8 subscales (27)</td>
</tr>
<tr>
<td></td>
<td>KDQOL-SF subscales scores</td>
<td>Increase by 7 to 19 points in 11/19 subscales (14)</td>
<td>No change in 10/11 subscales reported (31)</td>
</tr>
<tr>
<td></td>
<td>Nottingham Health Profile scores</td>
<td>—</td>
<td>No change in 5/6 subscales (27)</td>
</tr>
<tr>
<td></td>
<td>Dialysis and/or uremic symptoms</td>
<td>Decrease or disappearance (16,17,27,29,31)</td>
<td>No change (23)</td>
</tr>
<tr>
<td></td>
<td>Minutes to recovery after HD Utility</td>
<td>Decrease from 327 ± 203 to 30 ± 44 min (9)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase by 0.14 in Time Trade-Off (9)</td>
<td>No change in Health Utilities Index (9)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Systolic BP</td>
<td>Decrease by 7 to 23 mmHg (14,16,22–24,27,31)</td>
<td>Decrease (trend) (19)</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP</td>
<td>Decrease by 4 to 12 mmHg (16,22–24,31)</td>
<td>Decrease (trend) (19,27); no change (14)</td>
</tr>
<tr>
<td></td>
<td>Mean arterial pressure</td>
<td>Decrease by 3 to 12 mmHg (10,17,22,23,27,29)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>BP medication</td>
<td>Decrease by 20 to 70% (10,14,16,27)</td>
<td>Decrease (trend) (10,17,23,29,31)</td>
</tr>
<tr>
<td></td>
<td>Left ventricular hypertrophy</td>
<td>Decrease in LVMI by 29 to 38 g/m² (17,23); decrease in other measures (19,22,23)</td>
<td>—</td>
</tr>
<tr>
<td>Erythropoiesis</td>
<td>Hemoglobin</td>
<td>Increase by 1 to 1.5 g/dl (22,24)</td>
<td>Increase (trend) (19); no change (13,17,23)</td>
</tr>
<tr>
<td></td>
<td>Hematocrit</td>
<td>Increase by 1.2 to 5% (16,22,29,31)</td>
<td>Increase (trend) (14); no change (23)</td>
</tr>
<tr>
<td></td>
<td>Erythropoietin dose</td>
<td>Decrease by 32 to 47% (14,17,31)</td>
<td>Decrease (trend) (13,16,23,24,26)</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Protein intake</td>
<td>Increase by 25% (18)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Dry body weight</td>
<td>Increase by 1.7 to 2.0 kg (16,18,29)</td>
<td>Increase (trend) (19,27,31); no change (14,22,23)</td>
</tr>
<tr>
<td></td>
<td>Interdialytic weight gain/UF volume</td>
<td>Increase by 0.6 to 3.9 kg/vk (14,18)</td>
<td>Increase (trend) (10,23,27,29); no change (31)</td>
</tr>
<tr>
<td></td>
<td>Serum albumin</td>
<td>Increase by 0.2 to 0.6 g/dl (11,16,18,22,29)</td>
<td>Increase (trend) (19); no change (14,23,24,26)</td>
</tr>
<tr>
<td></td>
<td>nPNA</td>
<td>Increase by 0.1 g/kg per d (18)</td>
<td>No change (11,23,26)</td>
</tr>
<tr>
<td></td>
<td>Serum cholesterol</td>
<td>Increase by 31 mg/dl (26)</td>
<td>No change (16,19,22)</td>
</tr>
<tr>
<td>Mineral metabolism/ bone disease</td>
<td>Phosphate</td>
<td>Decrease by 1.2 mmol/L (30)</td>
<td>Decrease (trend) (24,26); no change (12,14,16,17)</td>
</tr>
<tr>
<td></td>
<td>Phosphate binder dose</td>
<td>Decrease by 38% (17)</td>
<td>Decreased (12); no change (14,16,27)</td>
</tr>
<tr>
<td></td>
<td>Aplastic bone disease</td>
<td>—</td>
<td>Decrease (trend) (30)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>Hospital admission rate</td>
<td>—</td>
<td>Decrease (relative risk = 0.6 to 0.7) (trend) (14)</td>
</tr>
<tr>
<td></td>
<td>Mean length of stay</td>
<td>—</td>
<td>Decrease by 26 to 40% (trend) (14)</td>
</tr>
</tbody>
</table>

PCS, Physical Components Summary score; MCS, Mental Components Summary score; KDQOL-SF, Kidney Disease Quality of Life Short Form Questionnaire; LVMI, left ventricular mass index; HD, hemodialysis; UF, ultrafiltration. Details on individual studies are provided in Table 2. All outcomes above are described at 3 to 24 mo of follow-up (majority at 12 mo). All studies with statistically significant findings are described in column 3, and all studies that evaluated the outcome but did not have statistically significant results are presented in column 4.

This study reports statistically significant decreases in hospital admission rate and length of stay at 6 yr of follow-up; here 1 yr data is described due to potential informative censoring after 1 yr (see text).
frequency of blood tests led to increased blood losses, but blood loss was not measured directly, and there was no change in iron dose or ferritin in this study (13). Four studies reported no change (14,17,24) or increase (29) in serum transferrin saturation or ferritin, but iron dose requirements were not specified.

Quantitative data on vascular access events were reported for seven cohorts and are summarized in Table 4. Definitions and outcomes varied considerably between studies. To facilitate describing of the results, we defined “access dysfunction” as any intervention to help to salvage the access and “permanent access failure” as any event that resulted in requirement of new access placement. A statistically significant decrease in access dysfunction was found for one cohort while on DHD compared with their time on conventional HD (16); 22 of the 72 patients in this study had survived for at least 12 mo. In another cohort, there were decreased permanent access failures for arteriovenous fistulae, compared with patients who were on conventional HD (21). Conversely, the remaining five cohorts reported no statistically significant differences in vascular access dysfunction or permanent failures with DHD compared with conventional HD at a mean follow-up of 3 to 24 mo (7,14,17,25,29).

Table 4. Summary of vascular access event rates from DHD Programs with five or more patients, 1998 to 2004

<table>
<thead>
<tr>
<th>Center/Reference</th>
<th>Daily Group</th>
<th></th>
<th>Control Group</th>
<th></th>
<th></th>
<th>RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-Up</td>
<td>Event Rate</td>
<td>Type</td>
<td>Follow-Up</td>
<td>Event Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Yr)</td>
<td>(per Yr)</td>
<td>Follow-Up</td>
<td>(Yr)</td>
<td>(per Yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All accesses combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turin, Italy (25)</td>
<td>50.9</td>
<td>0.28</td>
<td>Parallel</td>
<td>103.3</td>
<td>0.34</td>
<td>0.8</td>
<td>NS</td>
</tr>
<tr>
<td>multicenter, United States/ Europe (16)</td>
<td>238.6</td>
<td>0.05</td>
<td>Pre-post</td>
<td>50.5</td>
<td>0.28</td>
<td>0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mountain View, CA, USA (14)</td>
<td>68.9</td>
<td>0.94</td>
<td>Pre-post</td>
<td>37.5</td>
<td>1.01</td>
<td>0.9</td>
<td>NS</td>
</tr>
<tr>
<td>multicenter, United States (74)</td>
<td>34.0</td>
<td>0.79</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistulae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>London, Canada (7)b</td>
<td>NR</td>
<td>0.52 ± 1.47</td>
<td>Parallel</td>
<td>NR</td>
<td>0.18 ± 0.52</td>
<td>2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Mountain View, CA, USA (14)</td>
<td>15.3</td>
<td>0.59</td>
<td>Pre-post</td>
<td>90</td>
<td>0.27</td>
<td>2.2</td>
<td>NR</td>
</tr>
<tr>
<td>Lyon, France (17)</td>
<td>21</td>
<td>0.01</td>
<td>Pre-post</td>
<td>21</td>
<td>0.15</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>multicenter, United States (15)</td>
<td>21.1</td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous grafts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>London, Canada (7)b</td>
<td>NR</td>
<td>1.58 ± 1.79</td>
<td>Parallel</td>
<td>NR</td>
<td>2.12 ± 1.95</td>
<td>0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Mountain View, CA, USA (14)</td>
<td>44.9</td>
<td>1.16</td>
<td>Pre-post</td>
<td>24.7</td>
<td>1.13</td>
<td>1.0</td>
<td>NR</td>
</tr>
<tr>
<td>multicenter, United States (15)</td>
<td>8.75</td>
<td>1.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Catheters</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>London, Canada (7)b</td>
<td>NR</td>
<td>3.73 ± 4.42</td>
<td>Parallel</td>
<td>NR</td>
<td>4.51 ± 6.96</td>
<td>0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Mountain View, CA, USA (14)</td>
<td>8.8</td>
<td>0.46</td>
<td>Pre-post</td>
<td>5.2</td>
<td>1.53</td>
<td>0.3</td>
<td>NR</td>
</tr>
<tr>
<td>multicenter, United States (15)</td>
<td>4.2</td>
<td>1.44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent access failures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All accesses combined</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turin, Italy (25)</td>
<td>50.9</td>
<td>0.16</td>
<td>Parallel</td>
<td>103.3</td>
<td>0.14</td>
<td>1.1</td>
<td>NR</td>
</tr>
<tr>
<td>multicenter, United States (15)</td>
<td>31.3</td>
<td>0.12</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistulae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perugia, Italy (21)</td>
<td>7.6</td>
<td>0.02</td>
<td>Parallel</td>
<td>35.1</td>
<td>0.10</td>
<td>0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Catanzaro, Italy (19)</td>
<td>106.3</td>
<td>0.02</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR, relative risk; NR, not reported; NS, not significant.

*Follow-up is in total patient years, except for Mountain View (14), and Lyon (17), which reported total access-years. Similarly, event rates are reported as number per patient-year, except for Mountain View (14) and Lyon (17), which reported number per access-year.

*bLondon Study data include 12 patients on nocturnal HD.

A total of 31% of the 72 patients in this study survived for ≥1 yr, and 95% had an arteriovenous fistula.

Discussion

First proposed in 1968, DHD failed to gain widespread acceptance because of increased costs and inconvenience of scheduling for HD units. Since 1998, there has been resurgence in both in-center and home DHD programs throughout the world. Still an experimental therapy in most centers, governments are being pressured to fund home and in-center DHD as treatment options for patients with ESRD as a result of suggestions of substantial benefits on a variety of physiologic parameters and health-related quality of life.

We comprehensively summarized the current published evidence on DHD. Although each of the included studies reported significant, often substantial, improvement in at least one outcome with DHD, when reviewed together, the overall...
findings for individual outcomes were variable. The beneficial
effect of DHD on hypertension seemed to be relatively consist-
tent across studies, as did the absence of any effect of DHD on
phosphate control. However, health-related quality of life, erythropoiesis, and nutritional status improved significantly in
some studies but not in others. Measures of left ventricular hypertrophy improved in all four studies that evaluated this
outcome, but to what extent these improvements were due to
reductions in extracellular water versus actual reductions in
cardiac structural mass is unclear.

The included studies varied considerably with respect to
patient population; dialysis time, frequency, and location; def-
initions of similar outcomes; methods of outcome assessment;
follow-up times; and methodologic design. Moreover, the
delivered dialysis dose was not described in almost half of the
studies and may have differed between studies. This heteroge-
neity of previous studies of DHD likely is one factor contrib-
uting to the inconsistency of results observed.

Previous studies of DHD have also had several methodologic
limitations, potentially resulting in the irregular findings. Stud-
ies in this review had a median sample size of 23. Whether null
findings in some studies were due to lack of statistical power or
the absence of any effect of the therapy is uncertain. Con-
versely, the improvements that were observed in some studies
may have been exaggerated as a result of the use of nonideal
control groups. Outcomes on DHD were compared with a
concurrent control group for only four cohorts (7–13,21,23–25),
only one study of which used a randomized, crossover design
(23). The rest were pre–post case series with analyses of
changes in parameters from a baseline measurement on con-
ventional HD to follow-up measurements after initiation of
DHD. In these studies, because the comparative evaluations
were at different times without a concurrent control group,
confounding as a result of period effects, increased medical
attention and treatment, and placebo effects cannot be ruled
out. In the three studies with nonrandomized control subjects,
there was evidence of dissimilarities in baseline characteristics
between daily and conventional HD patients. In two of these
cohorts, the DHD patients were treated at home, whereas the
control group received dialysis in-center (7–13,21). Home HD
patients are a select group, generally characterized by excep-
tional compliance, motivation, and social support and lower
mortality risk compared with in-center patients after adjust-
ment for comorbid factors (61). Because of all of these limita-
tions, it is difficult to interpret the findings from DHD studies.

The utility of findings from previous studies is unclear. First,
the patients who underwent DHD in these studies are not
adequately representative of the general HD population. Most
patients were male and had been on dialysis for >2 yr. Ap-
proximately one fourth or fewer had diabetes, >90% had arte-
rivious fistulae or grafts, and almost half were selected to be
“stable” or able to undergo home HD. Thus, whether the gen-
eral HD population would achieve similar results as demon-
strated in these studies is not known. Second, likely as a result
of sample size constraints, the outcomes examined in previous
studies have been limited to health-related quality of life or
intermediate physiologic outcomes. No study has examined
mortality, and only one study assessed the effect of DHD on
hospitalization. Although this study suggests that hospitaliza-
tion rates and length of stay may be reduced by 30 to 40% with
DHD over 6 yr, interpretation of these data is limited by poss-
ible informative censoring and dropout biases.

The risks of DHD are also uncertain. Small sample size may
have impaired the detection of infrequent yet clinically signif-
icient adverse events in some studies; in others, it is difficult to
determine whether risks were evaluated properly. The relative
risk for vascular access events was evaluated in seven of 14
cohorts: Two reported decreases with DHD (16,21), whereas
two suggested a trend toward increased arteriovenous fistulae
events (7,14). All of these studies were subject to the method-
ologic limitations described above. With respect to blood loss
with DHD, the requirement for intravenous iron supplementa-
tion was reported in only one study and found to be increased
(27). Finally, the potential for patient fatigue and burnout is
concerning, particularly with in-center DHD, for which the
median discontinuation rate was found to be 41% by 3 to 24 mo
of follow-up.

Unfortunately, the data as reported in previous studies were
not sufficient to allow sample size calculations for a random-
ized trial. As mentioned, the majority of studies examined only
surrogate or self-reported outcomes. Moreover, although we
were able to gather estimates of the magnitude of effects that
were observed with DHD on surrogate and self-reported out-
comes, no study presented the variability of the change scores.
Thus, sample size calculations for a randomized trial would
require several assumptions and statistical simulations in ad-
inion to using the data presented here.

Limitations of this review should be appreciated. First, we were
not able to pool the data, given its substantial heterogeneity.
Second, to limit the scope of the review, we did not include studies
that evaluated costs of DHD. However, these data have been
reviewed previously (62,63). Third, we did not include abstracts
because of difficulties with accurate data abstraction. Finally,
although our methodologic assessment tool was based on accep-
ted criteria for evaluating studies of therapy (2), the tool itself has not
previously been validated. Because of this limitation, we did not
compare scores from individual studies. Rather, we developed
and used this tool simply as a means to summarize succinctly the
characteristics of the included studies.

The ESRD population has significantly impaired quality of life
compared with the general population (64–66) and experiences
tremendous morbidity. Moreover, the 20% annual mortality rate
in North America has not changed in more than a decade despite
advances in medical care (67). For several physiologic reasons (68),
DHD holds promise as a therapy that could improve the health of
this population. Unfortunately, our review indicates that previous
studies of DHD have been limited by inconsistent findings, small
sample size, nonideal control groups, selection and dropout bi-
ases, the absence of hard outcomes, and inadequate assessment of
potential risks. Thus, the available evidence does not support the
current widespread implementation of DHD, particularly in-cen-
ter DHD. A recent review resulted in similar conclusions regard-
ing nocturnal HD (69). Despite the methodologic limitations of
previous studies, however, the substantial improvements that
have been demonstrated in physiologic intermediate outcomes, as well as in health-related quality of life, cannot be ignored, especially given that no other therapy for this population has had such widespread dramatic effects. Further research in the way of large, methodologically rigorous studies is warranted. In the United States and Canada, two initiatives are now under way to address this need: The Quotidian Hemodialysis Registry (70) and the Frequent Hemodialysis Network randomized trials of frequent HD (http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-03–005.html). The latter is sponsored by the US National Institutes of Health, in conjunction with the Centers for Medicare and Medicaid Services. It is hoped that other governments will provide funding for additional studies of frequent HD to define better the role of these therapies in the treatment of ESRD.

Appendix 1: Description of Health-Related Quality-of-Life Instruments

Generic Medical Outcomes Survey—Short Form 36 (SF-36)

This generic, 36-item questionnaire was constructed to survey health status in the Medical Outcomes Survey and is now one of the most commonly used instruments to assess health-related quality of life in the world (71). Its 36 items assess eight health concepts: (1) limitations in physical activities because of health problems, (2) limitations in social activities because of physical or emotional problems, (3) limitations in usual role activities because of physical health problems, (4) bodily pain, (5) general mental health (psychologic distress and well-being), (6) limitations in usual role activities because of emotional problems, (7) vitality (energy and fatigue), and (8) general health perceptions. The scores can be reported as two summary scales: The Physical Components Summary and Mental Components Summary (72). The instrument may be either self- or interviewer-administered.

Kidney Disease Quality of Life—Short Form (KDQOL-SF)

This instrument includes the 36 items of the SF-36, as well as 43 additional kidney disease–specific items in 12 subscales (73,74). The long form of the instrument was originally developed to assess health-related quality of life in the HEMO study (75).

Nottingham Health Profile

Similar to the SF-36, this is a self-administered, generic instrument with 46 items that measures physical, social, and emotional health problems and their impact on functioning (76).

Time Trade-Off (TTO)

The TTO is a widely used method of measuring utility (77). The interviewer asks the respondent to value health states in terms of duration of life in a state of perfect health that would be equivalent to some period in a particular health condition, for example, the patient's own health state.

Health Utilities Index (HUI-3)

The HUI-3 is also a widely used instrument that assesses utility (78). The interviewer-administered version consists of 13 to 39 questions distributed among eight attributes: (1) vision, (2) hearing, (3) speech, (4) ambulation, (5) dexterity, (6) emotion, (7) cognition, and (8) pain. Utility is assessed using a health status classification system and a preference-based scoring formula.
early improvements persist in the mid and long term. *Hemodial Int* 8: 151–158, 2004


40. Ting GO: The case for short daily hemodialysis, why sDHD will be the predominant modality for frequent dialysis. *ASAIO J* 47: 443–445, 2001


54. Buoncristiani U: Fifteen years of clinical experience with


77. Torrance GW, Thomas WH, Sackett DL: A utility maximization model for evaluation of health care programs. *Health Serv Res* 7: 118–133, 1972