Mortality and Hospitalizations in Intensive Dialysis: A Systematic Review and Meta-Analysis

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Abstract

Background: Survival and hospitalization are critically important outcomes considered when choosing between intensive hemodialysis (HD), conventional HD, and peritoneal dialysis (PD). However, the comparative effectiveness of these modalities is unclear.

Objective: We had the following aims: (1) to compare the association of mortality and hospitalization in patients undergoing intensive HD, compared with conventional HD or PD and (2) to appraise the methodological quality of the supporting evidence.

Data Sources: MEDLINE, Embase, ISI Web of Science, CENTRAL, and nephrology conference abstracts.

Study Eligibility, Participants, and Interventions: We included cohort studies with comparator arm, and randomized controlled trials (RCTs) with >50% of adult patients (≥18 years) comparing any form of intensive HD (>4 sessions/wk or >5.5 h/session) with any form of chronic dialysis (PD, HD ≤4 sessions/wk or ≤5.5 h/session), that reported at least 1 predefined outcome (mortality or hospitalization).

Methods: We used the GRADE approach to systematic reviews and quality appraisal. Two reviewers screened citations and full-text articles, and extracted study-level data independently, with discrepancies resolved by consensus. We pooled effect estimates of randomized and observational studies separately using generic inverse variance with random effects models, and used fixed-effects models when only 2 studies were available for pooling. Predefined subgroups for the intensive HD cohorts were classified by nocturnal versus short daily HD and home versus in-center HD.

Results: Twenty-three studies with a total of 70,506 patients were included. Of the observational studies, compared with PD, intensive HD had a significantly lower mortality risk (hazard ratio [HR]: 0.67; 95% confidence interval [CI]: 0.53-0.84; I² = 91%). Compared with conventional HD, home nocturnal (HR: 0.46; 95% CI: 0.38-0.55; I² = 0%), in-center nocturnal (HR: 0.73; 95% CI: 0.60-0.90; I² = 57%) and home short daily (HR: 0.54; 95% CI: 0.31-0.95; I² = 82%) intensive regimens had lower mortality. Of the 2 RCTs assessing mortality, in-center short daily HD had lower mortality (HR: 0.54; 95% CI: 0.31-0.93), while home nocturnal HD had higher mortality (HR: 3.88; 95% CI: 1.27-11.79) in long-term observational follow-up. Hospitalization days per patient-year (mean difference: −1.98; 95% CI: −2.37 to −1.59; I² = 6%) were lower in nocturnal compared with conventional HD. Quality of evidence was similarly low or very low in RCTs (due to imprecision) and observational studies (due to residual confounding and selection bias).

Limitations: The overall quality of evidence was low or very low for critical outcomes. Outcomes such as quality of life, transplantation, and vascular access outcomes were not included in our review.

Conclusions: Intensive HD regimens may be associated with reduced mortality and hospitalization compared with conventional HD or PD. As the quality of supporting evidence is low, patients who place a high value on survival must be adequately advised and counseled of risks and benefits when choosing intensive dialysis. Practice guidelines that promote shared decision-making are likely to be helpful.

Abrégé

Contexte: Au moment de choisir une modalité de dialyse pour le traitement des patients souffrant d’insuffisance rénale, le taux de survie et la durée des hospitalisations sont des critères décisionnels d’une importance cruciale. Pourtant, l’efficacité différentielle de l’hémodialyse (HD) intensive, de l’HD conventionnelle et de la dialyse péritonéale (DP) demeure à ce jour mal connue.
Objectifs de l’étude : Nos objectifs allaient comme suit : 1) comparer le taux de mortalité et la durée des hospitalisations associés à chacune des modalités (HD intensive, HD conventionnelle et DP), et 2) évaluer la qualité méthodologique des données venant appuyer les résultats.

Sources : Les données proviennent des bases de données en ligne MEDLINE, EMBASE et ISI Web of Science, de même que de CENTRAL et de résumés de conférence en néphrologie.

Admissibilité à l’étude, participants et interventions : Ont été incluses à cette méta-analyse les études de cohorte comportant un volet comparatif et les essais contrôlés à répartition aléatoire comptant plus de 50 % de patients adultes et comparant n’importe quelle forme d’HD intensive (plus de 4 séances par semaine ou plus de 5,5 heures par séance) à n’importe quelle forme de dialyse chronique (DP ou HD à raison de 4 séances maximum par semaine ou de 5,5 heures maximum par séance). Les études retenues devaient également rapporter au moins un des deux critères décisionnels prédéfinis (mortalité et hospitalisation).

Méthodologie : Nous avons employé l’approche GRADE (Grading of Recommendations Assessment, Development and Evaluation). Cette approche s’applique aux revues systématiques et à l’évaluation de la qualité des données. Deux personnes ont passé en revue des citations et des articles complets pour en extraire les données relatives à l’étude. Les divergences ont été résolues par consensus. Nous avons regroupé les différentes mesures provenant des essais à répartition aléatoire et des études observationnelles pour ensuite les analyser, de façon isolée, à l’aide de la méthode générique de l’inverse de la variance avec modèles à effet aléatoire. Pour les données où seules deux études étaient disponibles pour le regroupement des données, nous avons plutôt employé la méthode générique de l’inverse de la variance avec modèles à effet fixe. Des sous-groupes avaient été prédéfinis dans les cohortes de patients traités par HD intensive, selon le moment (de jour ou de nuit) et le lieu (en centre de dialyse ou à domicile) du traitement.

Résultats : Cette méta-analyse compte 23 études totalisant 70 506 patients. Selon les études observationnelles, lorsque comparée à la DP, l’HD intensive était corrélée à un risque de mortalité significativement plus faible (HR=0,67; IC 95 0,53-0,84; I²=91 %). En comparaison avec l’HD conventionnelle, les schémas de traitement par HD intensive nocturne prodiguée à domicile (HR=0,46; IC 95 : 0,38-0,55; I²=0 %), nocturne en centre (HR=0,73; IC 95 : 0,60-0,90; I²=57 %) et de courte durée, de jour, à domicile (HR=0,54; IC 95 : 0,31-0,95; I²=82%) étaient corrélées à de plus faibles taux de mortalité. Des deux essais contrôlés à répartition aléatoire qui faisaient mention du taux de mortalité, l’HD diurne de courte durée en centre présentait le plus faible taux de mortalité (HR=0,54; IC 95 : 0,31-0,93) alors que l’HD nocturne à domicile présentait le taux de mortalité le plus élevé (HR=3,88; IC 95 : 1,27-11,79) selon les suivis observationnels faits à long terme. Le nombre de jours d’hospitalisation par année-patient (différence moyenne = -1,98 an; IC 95 : -1,59 à 2,37; I²=6 %) était plus faible chez les patients traités par HD intensive nocturne en comparaison avec ceux qui suivaient un traitement par la méthode conventionnelle. Dans tous les cas, la qualité des données recueillies s’est avérée faible ou très faible, qu’il s’agisse d’essais contrôlés à répartition aléatoire (en raison de l’imprécision) ou d’études observationnelles (en raison de facteurs de confusion et de biais de sélection).

Limites de l’étude : Dans l’ensemble, la qualité des données recueillies pour appuyer les critères décisionnels jugés essentiels s’est avérée faible ou très faible. De plus, des éléments tels que la qualité de vie du patient, la greffe et les enjeux liés à l’accès vasculaire n’ont pas été pris en compte dans notre revue systématique.

Conclusion : Le traitement de l’insuffisance rénale par HD intensive pourrait être associé à un taux de mortalité réduit et à des séjours à l’hôpital écourtés en comparaison avec les traitements par HD conventionnelle ou par DP. Cependant, en raison de la piètre qualité des données appuyant ces résultats, les patients qui accordent une grande importance à la survie devraient être adéquatement informés et conseillés sur les risques et les bienfaits offerts par l’HD intensive comme modalité de traitement. L’application de lignes directrices concernant la prise de décision conjointe en pratique clinique pourrait être pertinente.

Keywords
intensive hemodialysis, mortality, hospitalization, meta-analysis

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What was known before
Prior studies have yielded conflicting results on the effect of intensive hemodialysis on survival and hospitalization, related to differences in patient population and methodological issues such as selection bias and small sample size.

What this adds
We systematically reviewed the available evidence on the effect of intensive hemodialysis compared with conventional hemodialysis or peritoneal dialysis on survival and hospitalization, and applied the GRADE approach to appraise the quality of evidence. We found that intensive hemodialysis regimes may be associated with reduced mortality and hospitalization, compared with conventional hemodialysis or peritoneal dialysis, but with low or very low overall quality of evidence.

Introduction
Conventional hemodialysis (HD), comprised of 3 weekly sessions of 3-4-hour duration, remains the standard regimen for approximately 90% of prevalent dialysis patients in the United States. Although survival among HD patients in the United States has improved over time, long-term survival remains comparatively poor, with adjusted all-cause mortality rates up to 7.9 times that of the general Medicare population. Approximately 1% of all US HD patients die on intensive dialysis, delivered as either short daily (5-7 weekly sessions over 1.5-3 hours in duration) or nocturnal (3-7 weekly sessions over 6-8 hours in duration) treatments, in-center or at home. Intensive HD provides enhanced solute removal, and a growing body of evidence has suggested improvements in various physiological surrogate outcomes such as phosphate control, nutritional status, left ventricular mass, and anemia, suggesting that intensive regimens could potentially reduce the morbidity and mortality associated with HD. While conventional HD is the most common therapy, home and intensive HD therapies are becoming increasingly accessible, with more options for dialysis modalities from which patients can choose.

The comparative effects of dialysis regimens on mortality have been a major research priority for decades. While it has been argued that the dialysis comparative effectiveness research agenda should shift away from survival, and toward patient-reported outcomes, a recent international Delphi survey confirmed that both patients and health care professionals consider survival a critical outcome in dialysis treatment–related decision-making and research. Moreover, practice guidelines generally consider survival and morbidity-related events, such as hospitalization critical outcomes in formulating practice recommendations.

It is well recognized that studies reporting survival outcomes with intensive HD—both randomized trials and observational designs—have yielded conflicting results due to various factors, including differences in study populations and other methodological issues. For clinicians seeking to engage patients in shared decision-making around modality choice, these seemingly disparate findings are barriers to truly informed discussions of benefits and harms.

We therefore undertook this systematic review and meta-analysis of mortality and hospitalization comparing intensive HD with other dialytic therapies. Our primary objective was to use formal methodological quality appraisal methods to determine which bodies of evidence should be used to inform decision-making through future practice guidelines and patient decision-aids addressing modality selection.

Materials and Methods
See Appendix A for detailed methods. This article was prepared in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines. An experienced health information specialist developed the search strategies using terms to identify studies of intensive dialysis (see Appendix B for sample search strategy). We included cohort studies with comparator arm, and randomized controlled trials (RCTs) with >50% of adult patients (≥18 years) comparing any form of intensive HD (>4 sessions/wk or >5.5 h/session) with any form of chronic dialysis (peritoneal dialysis, HD ≤4 sessions/wk or ≤5.5 h/session), that reported at least 1 predefined outcome (mortality or hospitalization). We excluded studies of hemodiafiltration, hemofiltration, continuous renal replacement therapy, acute kidney injury, and pre-post studies with no separate patient cohort as a comparator arm. To reduce era effects, we excluded studies published before 2000. Two reviewers independently screened citations, evaluated the eligibility of each full-text article using prepiloted eligibility forms, and resolved discrepancies by consensus.

The 2 outcomes assessed were mortality and hospitalization, all-cause or cause-specific. Hospitalization was defined by either the admission rate or the number of days in hospital (per patient-year). We did not collect individual patient-level data. Two reviewers independently extracted study-level data from included studies using custom-made data extraction forms. For each outcome of interest, we extracted the unadjusted effect estimate, any adjusted effect estimates with factors included in the adjusted model, and methodological factors relevant to the quality appraisal. Disagreements in data collection were resolved by consensus.

Methodological Quality Appraisal
We applied the GRADE quality appraisal criteria summarized in GRADE evidence profile tables, which include risk of bias, indirectness, inconsistency, imprecision, and publication bias. For RCTs, risk of bias was assessed using criteria proposed by the Cochrane Collaboration.
observational studies, we used the modified Newcastle-Ottawa criteria proposed by the CLARITY Group.21

**Data Synthesis**

We planned to compute pooled effect estimates of randomized and observational studies separately, and used the $I^2$ statistic to quantify heterogeneity. We used mean differences to pool the continuous outcomes of hospitalization days/patient-year and hospitalization rates/patient-year, and used hazard ratios to pool the dichotomous outcome of mortality. We used a random effects model to account for within- and between-study heterogeneity when there were more than 2 pooled studies, and a fixed model when there were 2 studies.22 All statistical analyses were conducted using Review Manager (RevMan) Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

**Results**

**Study Characteristics**

Our search yielded 8198 citations. After excluding 1379 duplicates, 6819 citations were screened and 348 were reviewed in full-text. Twenty-three articles fulfilled all eligibility criteria and were included in the final review.23-45 (Figure 1), with a total of 70 506 reported patients (45 370 on conventional HD, 9582 on PD, and 15 444 on intensive dialysis). Three of the 23 included studies were RCTs,25,28,42 and the remaining 20 were observational cohort studies. Follow-up ranged from 1 to 23 years. Study population mean age ranged from 40.9 to 55.8 years in the intensive HD group, and from 40.9 to 62.4 years in the comparator group (conventional HD or PD) (Table 1). Definitions for intensive dialysis varied by study, with 8 studies of frequent short daily HD (ranging from 5 to 6 days per week) and 15 studies of long nocturnal HD (ranging from 5.0 to 10 hours per day).

**Results of Individual Studies**

Effect estimates for mortality and hospitalization in individual studies are described in Tables 2 and 3. Factors included in adjustment analysis varied across studies (Table 4).

i. Mortality: Thirteen studies23-35 examined mortality in intensive HD compared with conventional HD (2 RCTs and 11 observational studies). The 2 RCTs25,28 were long-term follow-up studies from the Frequent Hemodialysis Trials group, analyzed using intention-to-treat principles, but with inconsistent continuation of the randomization intervention. In a follow-up study to the Frequent Hemodialysis Network (FHN) short daily trial over a median of 3.6 years, Chertow et al described the relative mortality hazard for daily versus conventional HD as 0.54 (95% confidence interval [CI]: 0.31-0.93). Similarly, in a follow-up to the FHN nocturnal trial over a median of 3.7 years, Rocco et al described the relative mortality hazard for follow-up for nocturnal versus conventional HD as 3.88 (95% CI: 1.27-11.79). Of the remaining 11 observational studies, the adjusted hazard ratio (HR) for intensive HD compared with conventional HD ranged from 0.36 (95% CI: 0.22-0.61) to 0.87 (95% CI: 0.78-0.97).

Three observational studies examined mortality in intensive HD compared with PD.26,43,45 The adjusted HR for
Table 1. Baseline Characteristics of Included Studies.

| Author         | Year | Country            | Study duration, y | Study design | Funding source                                                                 | Sample size | Mean age, y (SD) | Dialysis regimen | Home vs in-center | % Prevental patients |
|----------------|------|--------------------|-------------------|--------------|--------------------------------------------------------------------------------|-------------|------------------|-------------------|--------------------|---------------------|
| **Mortality studies** |      |                    |                   |              |                                                                                  |              |                  |                   |                    |                     |
| Johansen NHD   | 2009 | USA                | 10 Pros.          | NIH          |                                                                                  | 94          | 47.0 (16.3)      | 46.7 (17.5)       | 7.5 ± 0.82         | 5.7 ± 0.44          | Home               | In-center           | 100                |
| Johansen SDHD  | 2009 | USA                | 10 Pros.          | NIH          |                                                                                  | 43          | 40.9 (17.3)      | 40.9 (19.1)       | 2.9 ± 0.59         | 5.4 ± 0.50          | Home               | In-center           | 100                |
| Lacson        | 2012 | USA                | 2 Pros.           | Fresenius Medical Care |                                                                                   | 746         | 52.8 (13.4)      | 54.1 (14.4)       | 7.85 ± 0.52        | 3 ± (NR)            | In-center          | In-center           | 100                |
| Chertow       | 2015 | USA                | 4 RCT             | NIH, NIDDK, CMS, DaVita, Dialysis Clinics, Fresenius Medical Care, Renal Advantage, Renal Research Institute, Satellite Healthcare |                                                                                   | 125         | 48.9 (13.6)      | 52.0 (14.1)       | 2.5 ± 0.33         | 5.17 ± 1.11         | In-center          | In-center           | 100                |
| Marshall NHD  | 2013 | Australia, New Zealand | 10 Pros.     | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care-Asia-Pacific Pty Ltd |                                                                                   | 714         | 51.1 (NR)        | 58.2 (NR)         | ≥5.0f              | ≥3×/wk              | Home               | In-center           | NR                 |
| Weinhandl     | 2012 | USA                | 3 Pros.           | NxStage Medical Inc |                                                                                   | 1873        | 52.2 (14.8)      | 53.2 (14.7)       | NR                 | 5-6 sessions per week | 3×/wk              | Home               | In-center           | 100                |
| Rocco         | 2015 | USA                | 3.7 RCT           | NIH, NIDDK, CMS | Baxter Healthcare Corporation, Gambro R&D, Fresenius Medical Care, and the Canadian Institutes for Health Research, Heart and Stroke Foundation of Ontario | 45          | 51.7 (14.4)     | 54.0 (12.9)       | ≥6                 | 5.06 ± 0.80         | 2.91 ± 0.21         | Home               | Home               | 100                |
| Nesrallah     | 2012 | Canada, France, USA | 10 Ret. Obs.     | Baxter Healthcare Corporation, Gambro R&D, Fresenius Medical Care, and the Canadian Institutes for Health Research, Heart and Stroke Foundation of Ontario |                                                                                   | 338         | 50.8 (12.4)      | 52.3 (12.4)       | 7.35 (0.87)        | 4.8 (1.1)           | 3×/wk              | Home               | 100                |
| Ok            | 2011 | Turkey             | 1 Pros.           | European Nephrology and Dialysis Institution (ENDI, Germany) |                                                                                   | 247         | 45.2 (13.9)      | 45.8 (12.9)       | 7.5 (0.33)         | 3.9 (0.11)          | 3×/wk              | In-center          | In-center           | 100                |
| Von Gersdorff | 2010 | Germany            | 3 Pros. Obs.      | NR            | European Nephrology and Dialysis Institution (ENDI, Germany) | 494         | 51 (15)         | 55 (15)          | 2.3 (0.5)          | NR                 | 3×/wk              | In-center          | NR                 |
| Kjellstrand Italy | 2008 | Italy              | 23 Pros.          | NR            | European Nephrology and Dialysis Institution (ENDI, Germany) | 165         | 51 (15)         | 55 (15)          | 2.3 (0.5)          | NR                 | 3×/wk              | In-center          | 91                 |
| Kjellstrand USA | 2008 | USA                | 23 Pros.          | NR            | European Nephrology and Dialysis Institution (ENDI, Germany) | 169         | 55 (15)         | 55 (15)          | 2.3 (0.5)          | NR                 | 3×/wk              | In-center          | 70%                |
| Kjellstrand France/UK | 2008 | France, UK       | 23 Pros.          | NR            | European Nephrology and Dialysis Institution (ENDI, Germany) | 81          | 55 (15)         | 55 (15)          | 2.3 (0.5)          | NR                 | 3×/wk              | In-center          | 88%                |
| Blagg         | 2006 | USA                | 2 Pros.           | NR            | European Nephrology and Dialysis Institution (ENDI, Germany) | 117         | 55.5 (NR)       | 55.5 (NR)        | 2.3-3.5            | ≥5×/wk             | 3×/wk              | Home               | NR                 |
| Lockridge     | 2011 | USA                | 12 Pros.          | NR            | European Nephrology and Dialysis Institution (ENDI, Germany) | 87          | 52 (15)         | 52 (15)          | 7 (1)              | NR                 | 3×/wk              | Home               | NR                 |
| Suri          | 2013 | Canada, USA, France | 10 Pros. Obs.     | CIHR           | European Nephrology and Dialysis Institution (ENDI, Germany) | 318         | 55.8 (18)       | 56 (13)          | 2.7 (0.7)          | 5.8 (0.5)           | 3×/wk              | In-center          | 100                |

(continued)
| Author            | Year | Country       | Study duration, y | Study design | Funding source                                                                 | Sample size | Mean age, y (SD) | Dialysis regimen                              | Home vs in-center | % Prevalent patients |
|-------------------|------|---------------|-------------------|--------------|--------------------------------------------------------------------------------|-------------|------------------|-----------------------------------------------|-------------------|---------------------|
| Marshall*         | 2013 | Australia, New Zealand | 10 Pros. Obs. | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd | 714 | 2649 | 51.1 (NR) | 60.4 (NR) | ≥5.0 h | ≥3×/w k | PD | ~ | ~ | NR |
| Nesrallah         | 2016 | USA           | 12 Ret. Obs.     |              | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd | 2668 | 2668 | 51.3 (14.3) | 51.4 (14.1) | 1.5-3 h | 5-7 | PD | Home | ~ | ~ | 100 |
| Weinhandl*        | 2016 | USA           | 3 Ret. Obs.      |              | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd | 4201 | 4201 | 53.8 (14.9) | 54.6 (15.0) | NR | 5-6 | PD | Home | ~ | ~ | 100 |
| **Hospitalization studies** |     |               |                  |              | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd |     |     |     |     |     |     |     |     |     |     |     |     |
| Van Eps           | 2010 | Australia     | 3 Pros. Obs.     | NHMRC        | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd | 63 | 172 | 51.7 (12.9) | 58.3 (15.5) | 6-9 | 3.5-5 | 3×/w k | Home | In-center | 100 |
| Lindsay           | 2003 | Canada        | 2.5 Pros. Obs.   | NHMRC        | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd | 12 | 17 | 44.2 (6.4) | 48.8 (11.9) | 6-9 | 3-5 | 3×/w k | Home | In-center | 100 |
| Bergman           | 2008 | Canada        | 2 Pros. Obs.     | Heart and Stroke Foundation, Physician Services Incorporated Foundation | 32 | 42 | 43 (2) | 44 (2) | 8-10 | 5-6 | 3×/w k | Home | In-center | 100 |
| Zimbudzi          | 2014 | Australia     | 1 Ret. Obs.      | NHMRC        | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd | 25 | 25 | 53.6 (NR) | 47.4 (NR) | 8× | 4 | 3×/w k | Home | In-center | 100 |
| Lacson            | 2010 | USA           | 1 Pre-post Obs.  | Fresenius Medical Care | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd | 655 | 15 334 | 51.2 (12.7) | 62.4 (15.0) | 7.85 ± 0.48 | 3 | 3×/w k | In-center | In-center | 100 |
| Weinhandl*        | 2015 | USA           | 5 Ret. Obs.      | NxStage Medical Inc | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd | 2084 | 10 420 | 540 (NR) | 54.3 (NR) | NR | 5-6 | 3×/w k | Home | In-center | 100 |
| Culleton          | 2007 | Canada        | 2 RCT Obs.       | Kidney Foundation of Canada | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd | 26 | 25 | 53.1 (12.4) | 53.1 (13.4) | 6 | 5-6 | 3×/week | Home | In-center | 100 |
| Kumar             | 2008 | USA           | 5 Pros. Obs.     | NHMRC        | Abbott Australasia Pty Ltd, Roche Products NZ Ltd, Novartis NZ Ltd & Fresenius Medical Care–Asia-Pacific Pty Ltd | 22 | 22 | 64 | 52 (4) | 3 | 2.45 (0.3) | 5.4 (0.5) | PD | Home | ~ | 23 |

Note: HD = hemodialysis; PD = peritoneal dialysis; NHD = nocturnal hemodialysis; SDHD = short daily hemodialysis; NR = not reported. Pros. Obs = Prospective Observational Ret. Obs = Retrospective Observations

NHMRC = National Health and Mental Research Council
NIH = National Institutes of Health
NIDDK = National Institute for Diabetes and Digestive Diseases
CMS = Centers for Medicare and Medicaid Services
CIHR = Canadian Institutes for Health Research

1Hospitalization outcomes also reported.
2Most contemporary reported cohort.
3In 95% of sample.
4In 99% of sample.
5In 94% of sample.
6Median.
7In 61% of sample.
Table 2. Mortality Event Rates From Individual Studies.

| Author/year         | Sample size | Event rate, per patient-year | Unadjusted effect estimate | Adjusted effect estimate |
|---------------------|-------------|------------------------------|----------------------------|--------------------------|
|                     | Intensive   | Control                      | Intensive                  | Control                  | HR (95% CI) | P value | HR (95% CI) | P value |
| **Intensive HD vs conventional HD** |
| Mortality           |
| Johansen NHD 2009   | 94          | 0.074                        | 0.154                      | NR                       | NR          | 0.36 (0.22-0.61) | .0001 |
| Johansen SDHD 2009  | 43          | 0.091                        | 0.139                      | NR                       | NR          | 0.64 (0.31-1.31) | .22   |
| Lacson 2012         | 746         | 0.142                        | 0.557                      | 0.69 (0.58-0.84)         | <.001       | 0.75 (0.61-0.91) | .004  |
| Marshall NHD 2013   | 714         | 0.061                        | 0.061                      | 0.4 (0.33-0.49)          | <.05        | 0.46 (0.37-0.56) | <.05  |
| Weinhändl 2012      | 1873        | 0.110                        | 0.127                      | NR                       | NR          | 0.87 (0.78-0.97) | .01   |
| Nesrallah 2012      | 338         | 0.061                        | 0.105                      | 0.39 (0.29-0.52)         | NR          | 0.55 (0.34-0.87) | .01   |
| Ok 2011             | 247         | 0.0177                       | 0.0623                     | 0.28 (0.09-0.85)         | .02         | 0.68 (0.1-0.98) | .04   |
| Von Gersdorff 2010  | 494         | 0.031                        | 0.066                      | NR                       | NR          | 0.75 (NR)        | <.03  |
| Kjellström-Italy 2008 | 165      | NR                           | 0.066                      | NR                       | NR          | 0.34 (0.20-0.54) | <.001 |
| Kjellström-USA 2008 | 169         | NR                           | 0.143                      | NR                       | NR          |             |       |
| Kjellström-France/UK 2008 | 81    | NR                           | 0.048                      | NR                       | NR          |             |       |
| Blagg 2006          | 117         | NR                           | 0.076                      | NR                       | NR          | 0.39 (0.19-0.51) | <.005 |
| Lockridge 2011      | 87          | NR                           | 0.0453                     | NR                       | NR          | 0.30 (NR)       | NR    |
| Suri 2013           | 318         | 0.156                        | 0.109                      | 1.6 (1.1-2.3)            | .023        | 1.3 (1.02-1.7) | .034  |
| **Hospital admission rate (admissions per patient-year)** |
| Ok 2011             | 247         | 0.65                         | 2.26                       | NR                       | NR          |             |       |
| Lindsay-NHD 2003    | 12          | 0.95 ± 1                     | 0.93 ± 1.2                 | NR                       | NR          |             |       |
| Van Eps 2010        | 63          | 2.0 (1.7-2.3)                | 1.75 (1.54-1.98)           | NR                       | NR          |             |       |
| Bergman 2008        | 32          | 0.21 ± 0.07                  | 0.49 ± 0.12                | NR                       | NR          |             |       |
| Zimudzi 2014        | 25          | 0.72                         | 0.72                       | NR                       | NR          |             |       |
| Lacson 2010         | 655         | 1.26                         | 1.74                       | NR                       | NR          |             |       |
| Weinhändl 2015      | 2084        | 1.78                         | 1.69                       | NR                       | NR          | 1.03 (0.99-1.08) | NR   |
| Johansen NHD 2009   | 94          | 1.1                          | 0.9                        | NR                       | NR          |             |       |
| Johansen SDHD 2009  | 43          | 0.6                          | 0.7                        | NR                       | NR          |             |       |
| **Hospitalization day rate (hospital days per patient-year)** |
| Lindsay-NHD 2003    | 12          | 4.8 ± 7                      | 4.54 ± 6.5                 | NR                       | NR          |             |       |
| Van Eps 2010        | 63          | 9.2 (8.6-9.9)                | 11.61 (11.06-12.19)        | NR                       | NR          |             |       |
| Bergman 2008        | 32          | 1.49 ± 0.66                  | 3.37 ± 1.03                | NR                       | NR          |             |       |
| Zimudzi 2014        | 25          | 2.8 (NR)                     | 3.4 (NR)                   | NR                       | NR          |             |       |
| Lacson 2010         | 655         | 9.6 (NR)                     | 13.5 (NR)                  | NR                       | NR          |             |       |
| Weinhändl 2015      | 2084        | 9.64                         | 9.91                       | NR                       | NR          | 1.01 (0.94-1.07) | NR   |
| Johansen NHD 2009   | 94          | 5.8 (NR)                     | 5.6 (NR)                   | NR                       | NR          |             |       |
| Johansen SDHD 2009  | 43          | 3.1 (NR)                     | 3.1 (NR)                   | NR                       | NR          |             |       |
| **Intensive HD vs PD** |
| Mortality           |
| Weinhändl 2016      | 4201        | 0.121                        | 0.151                      | NR                       | NR          | 0.8 (0.73-0.87) | <.001 |
| Nesrallah 2016      | 2668        | 0.127                        | 0.167                      | 0.84 (0.82-0.86)         | <.001       | 0.75 (0.68-0.82) | <.001 |
| Marshall PD 2013    | 714         | 0.35 (0.26-0.43)             | 0.45 (0.37-0.56)           | <.05                     |             |             |       |
| **Hospital admission rate (admissions per patient-year)** |
| Kumar 2008          | 22          | 0.68 (NR)                    | 0.76 (NR)                  | 0.78                     | .5          | 0.98         | .9    |
| Weinhändl 2016      | 4201        | 1.74                         | 1.99                       | NR                       | NR          | 0.92 (0.89-0.95) | NR    |
| **Hospitalization day rate (hospital days per patient-year)** |
| Kumar 2008          | 22          | 3.3                          | 5.6                        | 0.37                     | .06         | 1.23         | .8    |
| Weinhändl 2016      | 4201        | 10.27                        | 12.67                      | 0.81                     | 0.75-0.87   | NR           |       |

Note. CI = confidence interval; HR = hazards ratio; NHD = nocturnal hemodialysis; SDHD = short daily hemodialysis; NR = not reported.

*Reported as absolute number of events.

Intensive HD compared with PD varied from 0.45 (95% CI: 0.37-0.56) to 0.8 (95% CI: 0.73-0.87).

Hospitalization: One RCT\textsuperscript{42} reported adverse events of mean hospitalizations per patient from baseline to study exit in both the nocturnal (0.62; 95% CI: 0.24-1.00) and conventional HD groups (0.84; 95% CI: 0.18-1.50) (Tables 2 and 3).

Ten observational studies reported hospitalization rates. Eight compared intensive HD with conventional HD,\textsuperscript{23,30,36-41} and 2 compared intensive HD with PD\textsuperscript{35,44} (Tables 2 and 3).
Table 3. Mortality Event Rates From Randomized Controlled Trials.

| Author/year | Sample size | Event rate, per patient-year | Unadjusted effect estimate | Adjusted effect estimate |
|-------------|-------------|------------------------------|---------------------------|-------------------------|
|             | Intensive   | Control                      |                           |                         |
|             | Intensive   | Control                      | Unadjusted effect estimate| Adjusted effect estimate |
|             | HR (95% CI) | P value                      | HR (95% CI)               | P value                 |
| Intensive HD vs conventional HD | | | | |
| Mortality   | | | | |
| Chertow 2015 | 125 | 120 | 20<sup>a</sup> | 34<sup>a</sup> | NR | NR | 0.54 (0.31-0.93) | NR |
| Rocco 2015  | 45  | 42  | 14<sup>a</sup> | 5<sup>a</sup> | NR | NR | 3.88 (1.27-11.79) | .01 |
| Hospital admission rate<sup>b</sup> | | | | |
| Culleton 2007 | 26  | 25  | 0.62 (0.24-1.00)<sup>a</sup> | 0.84 (0.18-1.50)<sup>a</sup> | NR | NR | NR | NR |

Note. CI = confidence interval; HR = hazards ratio; NR = not reported.
<sup>a</sup>Reported as absolute number of events.
<sup>b</sup>Mean rate per patient from baseline to study exit (study duration August 2004 to December 2006).

Only 3 of these studies also reported an unadjusted and/or adjusted relative treatment effect estimate comparing intensive HD with PD or conventional HD.<sup>41,43,44</sup>

**Synthesis of Results**

Due to incomplete data reporting, only 13 of the 23 studies in this systematic review were included in the meta-analysis<sup>23,26,27,29,30,32,33,36-38,43,45,46</sup> (Figures 2-7 and Tables 5-8).

i. Nocturnal HD versus conventional HD: Three observational studies<sup>23,26,29</sup> reported risk of all-cause mortality in nocturnal home HD compared with conventional HD, with a pooled hazard ratio of 0.46 (95% CI: 0.38-0.55; I² = 0%), favoring nocturnal home HD over conventional HD. Two observational studies<sup>30,46</sup> reported risk of all-cause mortality in nocturnal in-center HD compared with conventional HD, and favored nocturnal in-center HD (HR: 0.73; 95% CI: 0.60-0.90; I² = 57%). Only 1 RCT<sup>28</sup> by Rocco et al reported mortality in this patient group, precluding pooling.

Three studies<sup>36-38</sup> reported mean hospitalization days per patient-year in nocturnal home HD compared with conventional HD, with a pooled mean difference of −1.98 (95% CI: −2.37 to −1.59; I² = 6%) favoring nocturnal HD. The mean hospital admission rate per patient-year favored nocturnal home HD, with a pooled mean difference of −0.04 (95% CI: −0.46 to 0.38; I² = 77%).

ii. Short Daily HD versus conventional HD: Four studies<sup>23,27,32,33</sup> reported risk of all-cause mortality in short daily home HD compared with conventional HD, and favored short daily home HD (HR: 0.54; 95% CI: 0.31-0.95; I² = 82%).

One observational study<sup>35</sup> by Suri et al and one RCT<sup>25</sup> by Chertow et al compared short daily, in-center HD with conventional HD, precluding pooling of estimates for this predefined group.

iii. Intensive HD versus PD: Three studies<sup>26,43,45</sup> reported risk of all-cause mortality in intensive HD compared with PD (2 examined nocturnal home HD, and 1 examined short daily, home HD). Pooled HR was 0.67 (95% CI: 0.53-0.84; I² = 57%) favoring intensive HD over PD.

The remainder of studies in predefined patient groups did not report adequate data such as measures of dispersion, precluding pooling.

**Methodological Quality**

Tables 5 to 8 summarize the quality appraisal by predefined patient groups on an outcome-by-outcome basis. RCTs assessed outcomes of mortality and hospitalization rate in nocturnal home HD. Quality of evidence for the RCTs assessing mortality was low (imprecision). Quality of evidence for the RCT assessing hospitalization rate was also low (imprecision and risk of bias due to lack of blinding). For observational studies, risk of bias was serious in all pooled estimates. Concern for risk of bias was due to incomplete adjustment for all important prognostic factors and selection of exposed and unexposed cohorts from different populations (Appendix C). Inconsistency (due to heterogeneity from study design, study population characteristics, treatment indication, or unexplained heterogeneity) and imprecision (due to small sample size or CIs overlapping no effect) also affected the quality of most estimates. Small numbers of included studies in any predefined patient group precluded meaningful analysis of publication bias by funnel plots. The overall quality of evidence was low or very low for critical outcomes.

**Discussion**

To our knowledge, this is the first systematic review and meta-analysis of mortality and hospitalization in intensive HD compared with conventional HD and PD. Compared with conventional HD, nocturnal home HD, nocturnal in-center HD, and short daily home HD were all significantly
Table 4. Factors Adjusted and Not Adjusted for in Multivariable Analysis and/or Study Design.

| First Author | Year | Age | BMI | Comorbid conditions* | Country | Diabetes | Dialysis vintage | Dry weight | Education | ESRD start date | ESRD duration | Ethnicity | Gender | GFR | HD dose | HD session length | Hemoglobin | Hospitalization | Medicaid status | Primary diagnosis | Race | Smoking | Dialysis modality | Time on HD | Vascular access | LVM | Urine volume |
|---------------|------|-----|-----|----------------------|---------|----------|------------------|------------|-----------|----------------|---------------|-----------|--------|-----|------|------------------|------------|----------------|---------------|-----------------|-------|---------|-----------------|------------|-----------------|-----|----------|
| Johansen      | 2009 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Lacson        | 2010 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Lacson        | 2012 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Nesrallah     | 2012 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| OK            | 2010 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Sun           | 2012 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Von           | 2010 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Gersdorff     |      |     |     |                      |         |           |                  |            |           |                |               |           |         |     |     |                 |            |                |               |                 |        |         |                 |            |                |     |          |
| Kjellstrand   | 2008 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Blagg         | 2006 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Lindsay       | 2003 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Lockridge     | 2011 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Van Eps       | 2010 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Bergsma       | 2008 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Weinhandl     | 2014 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Marshall      | 2013 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Nesrallah     | 2016 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Weinhandl     | 2016 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Kumar         | 2008 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Weinhandl     | 2012 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |
| Zimbudt       | 2014 | √   | √   | √                    | √       | √        | √                | √          | √         | √              | √             | √         | √       | √   | √    | √                | √          | √              | √             | √               | √     | √       | √               | √          | √               | √   | √        |

Note. BMI = body mass index; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HD = hemodialysis; LVM = left ventricular mass.

*Additionally adjusted for Charlson comorbidity index; cardiovascular-related, myocardial infarction; congestive heart failure; peripheral vascular disease; cerebrovascular disease; hyperparathyroidism; and cancer.

Did not adjust for any factors.

*Additionally adjusted for Charlson Comorbidity Index, cardiovascular-related, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hyperparathyroidism, and cancer.
associated with decreased mortality. Intensive HD was also significantly associated with decreased mortality when compared with PD. With respect to hospitalization outcomes, nocturnal home HD was significantly associated with decreased rate of hospitalization days per year, but had no appreciable association with the rate of hospital admissions per year. The overall quality of evidence for these outcomes was similarly low across observational studies (primarily due to residual confounding and selection bias) and RCTs (primarily related to imprecision due to small
study populations and low event rates) for a given modality comparison.

Among the studies reporting outcomes with nocturnal home HD, one RCT by Rocco et al reported higher mortality in patients on nocturnal home HD versus conventional HD. In contrast, our pooled analysis of observational studies found reduced mortality with home nocturnal HD. Reasons for this discrepancy may include the following: (1) The RCT was not powered to detect differences in mortality alone, and observed differences in patient survival could be explained by chance alone; (2) RCT conventional HD participants had a very low death rate of 0.032 events per patient-year, 5-fold lower compared with HD patients in the US Renal Data System, thus increasing the risk of type I error; (3) frequent modality changes over long-term follow-up precluded attributing causality to the baseline dialysis regimen—the as-treated analysis of the FHN nocturnal cohorts using the prior 6-month average exposure in fact found no significant difference in long-term survival; (4) in the observational studies, patients who selected home nocturnal HD represent a healthy population with lower mortality risk, with residual confounding remaining despite statistical adjustment; and (5) loss of residual renal function in the predominantly incident nocturnal HD patients of the RCT (median dialysis vintage 0.9 years) may have contributed to their observed increased mortality.48,49 The observational studies in our pooled analysis of observational studies included only incident conventional HD patients, while intensive HD patients were all prevalent patients. Loss of residual kidney function in the conventional HD group may have contributed to their observed increased mortality.

Among the studies reporting on short daily HD patients treated in-center, we identified only one observational study and one RCT. Using international registry data and a matched cohort design, Suri et al reported higher mortality with in-center short daily HD compared with conventional HD (very low quality of evidence due to risk of bias from incomplete risk adjustment). Conversely, in the long-term follow-up study of FHN daily trial participants, Chertow et al reported lower mortality for in-center short daily HD patients (moderate quality of evidence—rated down one level for imprecision). However, patients in the study by Suri et al were older, had more comorbidities, had a high overall mortality rate, and were typically prescribed daily HD as a “salvage” therapy. Their higher death rate compared with matched controls may have been due to incomplete risk adjustment for disease severity, frailty, and other factors. Conversely, patients in the FHN daily study were healthier and younger and clinical trial participants with an unusually low death rate of only 4% in the first year. These studies therefore inform clearly different clinical effectiveness questions.

Our pooled results also indicated that intensive HD was associated with a lower mortality than PD (very low quality evidence due to risk of bias and inconsistency). All 3 studies included in the meta-analysis examined a home intensive HD regimen with PD, and used advanced modeling and matching techniques to account for measured between-group case-mix differences. Unmeasured potent prognostic factors such as self-efficacy or functional ability may have resulted in some residual confounding favoring home intensive HD. The available data did not enable a subgroup analysis evaluating the effects of a PD-first approach among patients who later switch to intensive home HD.

We identified only 1 RCT examining hospitalization in intensive HD, which precluded pooling. Our meta-analysis of studies examining hospitalization outcomes found that intensive HD was associated with a lower number of hospitalization days per patient-year. This is in line with findings by Ting et al (excluded for no comparator group), where 42 patients who were converted from conventional HD to short daily HD had a 34.4% reduction in hospitalization days. For intensive HD patients who dialyze at home, greater self-efficacy may have facilitated earlier discharge from hospital.

It is important to note that the intervention of intensive HD itself may confer complications beyond those included in our review. Increased access frequency has been associated with complications including need for thrombectomy and surgical revision. Alternate needling methods, such as buttonhole cannulation, may be associated with increased risk of infection. Long hours of nocturnal HD may lead to electrolyte imbalances (hypokalemia, hypophosphatemia), and fluid removal associated hypotension with organ ischemia. More frequent or long hours of exposure of blood to the
Table 5. GRADE Evidence Profile Table: Effects of Nocturnal Home HD Compared With Conventional HD in Patients on Chronic HD.

| Quality assessment | No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Nocturnal home hemodialysis | Conventional hemodialysis | Relative (95% CI) | Absolute (95% CI) | Quality | Importance |
|--------------------|----------------|--------------|--------------|---------------|--------------|-------------|----------------------|---------------------------|--------------------------|-----------------|-----------------|----------|------------|
| All-cause mortality in observational studies | 3 | Observational studies | Serious<sup>a</sup> | Not serious | Not serious | Strong association | —/1146 | —/5936 | HR 0.46 (0.38-0.55) | — | ★★★ | Low | Critical |
| All-cause mortality in randomized trials | 1 | Randomized trials | Serious<sup>b</sup> | Not serious | Not serious | Serious<sup>d</sup> | None | 14/45 (31.1%) | 5/42 (11.9%) | HR 3.88 (1.27-11.79) | 269 more per 1000 (from 30 more to 657 more) | ★★★ | Low | Critical |
| Mean hospital days in observational studies (assessed with hospital days per patient-year) | 3 | Observational studies | Serious<sup>a</sup> | Not serious | Not serious | Serious<sup>e</sup> | None | 107 | 231 | — | MD 1.98 lower (2.37 lower to 1.59 lower) | ★★★ || Very low | Critical |
| Mean hospitalization rate in observational studies (assessed with hospitalizations per patient-year) | 3 | Observational studies | Serious<sup>a</sup> | Serious<sup>f</sup> | Not serious | Serious<sup>e</sup> | None | 107 | 231 | — | MD 0.04 lower (0.46 lower to 0.38 higher) | ★★★ || Very low | Critical |
| Mean hospitalization rate in randomized trials (assessed with hospitalizations per patient-year) | 1 | Randomized trials | Serious<sup>b</sup> | Not serious | Not serious | Serious<sup>e</sup> | None | 27 | 25 | — | MD 0.22 lower | ★★★ | Low | Critical |

Note. CI = confidence interval; HR = hazard ratio; MD = mean difference.

<sup>a</sup>Risk of bias due to incomplete adjustment for prognostic factors in statistical analysis.

<sup>b</sup>Absolute event counts not provided, precluding estimation of absolute event rates.

<sup>c</sup>Extremely low control group event rate suggests uneven baseline prognosis between treatment groups.

<sup>d</sup>Low event rates and small overall sample size reduce precision for this outcome; optimal information size criterion not met.

<sup>e</sup>Small sample size; observed effect may be due to random error.

<sup>f</sup> $I^2 = 77\%$ for pooled effect estimate, possibly due to unexplained heterogeneity in study population and study design.

<sup>g</sup>CI overlaps, no effect.

<sup>h</sup>Lack of blinding may have biased hospitalization practices and adjudication of hospitalization events.
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Strengths of our study include the use of rigorous systematic review and quality appraisal methods, resulting in evidence summaries that are usable by a range of audiences. Our study’s limitations are primarily those of the included studies as described in our quality appraisal. Additional potential limitations include the following: (1) Our a priori definitions of eligible intensive dialysis prescriptions may have resulted in exclusion of some studies; (2) we identified some variability in dialysis technology, including the use of low-flow dialysate systems, which may have introduced clinical heterogeneity in our meta-analyses; and (3) our findings should not be extrapolated to patients outside of the inclusion criteria of the RCTs and observational studies in this review, which generally include nonpregnant, maintenance HD patients without mental incapacity, medical contraindications to intensive dialysis, or short lifespan (eg, less than 6 months). In addition, the FHN Short Daily study excluded patients with residual kidney function of greater than 3 mL/min per 35 L. Finally, we did not study quality of life, transplantation, and vascular access outcomes, and cannot issue general guidance regarding modality choice and these critical outcomes.

Based on our findings, we recommend several future avenues of research and work. First, clinical practice guidelines and decision-aids addressing dialysis modality selection with an emphasis on shared-decision making are needed. While strong recommendations based on high-quality evidence are desirable, guidelines can be most useful when there is less certainty surrounding treatment effects. When confidence in treatment effect measures is low, guideline statements will typically be qualified or “conditional,” and provide direction

Table 6. GRADE Evidence Profile Table: Effects of Nocturnal In-Center HD Compared With Conventional HD in Patients on Chronic HD.

| Quality assessment | No. of patients | Effect |
|--------------------|----------------|--------|
| No. of studies     | Study design   | Risk of bias | Consistency | Indirectness | Imprecision | Other considerations | Nocturnal in-center HD | Conventional HD | Relative (95% CI) | Absolute (95% CI) | Quality | Importance |
| Mortality          | 2              | Observational studies | Serious | Serious | Not serious | Not serious | None | −/993 | −/3209 | HR 0.73 (0.60 to 0.90) | −1 | ⊕⊕⊕⊕ | Critical |

Note. HD = hemodialysis; CI = confidence interval; HR = hazard ratio.

Some concern for incomplete adjustment for prognostic factors in statistical analysis.

I² = 57% for pooled effect estimate, could not exclude heterogeneity due to study design.

Absolute event counts not provided, precluding estimation of absolute event rates.

Table 7. GRADE Evidence Profile Table: Effects of Short Daily Home HD Compared With Conventional HD in Patients on Chronic HD.a

| Quality assessment | No. of patients | Effect |
|--------------------|----------------|--------|
| No. of studies     | Study design   | Risk of bias | Consistency | Indirectness | Imprecision | Other considerations | Short daily home HD | Conventional HD | Relative (95% CI) | Absolute (95% CI) | Quality | Importance |
| Mortality          | 4              | Observational studies | Serious | Serious | Not serious | Not serious | None | −/2448 | −/9795 | HR 0.54 (0.31 to 0.95) | −1 | ⊕⊕⊕⊕ | Critical |

Note. Only 1 study compared short daily in-center HD with conventional HD, precluding pooling. HD = hemodialysis; CI = confidence interval; HR = hazard ratio.

Concerns that selection of exposed and unexposed from different population, and concern for residual confounding.

I² = 82% for pooled effect estimate, possibly due to unexplained heterogeneity in study design.

Absolute event counts not provided, precluding estimation of absolute event rates.

Table 8. GRADE Evidence Profile Table: Effects of Intensive HD Compared With PD in Patients on Chronic HD.

| Quality assessment | No. of patients | Effect |
|--------------------|----------------|--------|
| No. of studies     | Study design   | Risk of bias | Consistency | Indirectness | Imprecision | Other considerations | Intensive HD | PD | Relative (95% CI) | Absolute (95% CI) | Quality | Importance |
| Mortality          | 3              | Observational studies | Serious | Serious | Not serious | Not serious | None | −/7583 | −/9538 | HR 0.67 (0.53 to 0.84) | −1 | ⊕⊕⊕⊕ | Critical |

Note. HD = hemodialysis; PD = peritoneal dialysis; CI = confidence interval; HR = hazard ratio.

Concern for lack of matching on prognostic factors and adjustment in statistical analysis.

I² = 91% for pooled effect estimate, with unexplained heterogeneity possibly due to study design and population.

Absolute event counts not provided, precluding estimation of absolute event rates.
not on a specific treatment option, but rather on how clinicians should engage patients in shared decision-making, including which values and preferences to elicit when considering a pair of treatment alternatives.58 Second, our review findings challenge the notion that all dialysis modalities provide similar outcomes. Currently, the only modality selection guideline published to date endorses a “modality-neutral” approach, in which patients are advised to focus on preferences rather than outcomes.59 However, our findings suggest that some fully informed and highly motivated patients may consider more intensive regimens. Patients who place a very high value on survival may choose an intensive HD regimen despite the increased effort and despite the uncertainty in the published evidence. Thus, comparative effectiveness research of dialysis modalities is needed to aid in reducing uncertainty around candidate treatment alternatives, and obtaining truly informed consent. Third, international standards for patient decision-aids have been established and the inclusion of up-to-date quality-appraised evidence summaries of dialysis modality selection in these knowledge products is considered essential to truly informed patient choice.60 Finally, studies evaluating the effects of intensive dialysis for patients with specific clinical indications (frailty, severe heart disease, restoring fertility, improving obstetrical outcomes) would be of significant value.

Conclusion

Home and intensive HD therapies continue to proliferate globally, calling on more clinicians to engage patients in discussing increasingly complex treatment decisions. We found the quality of supporting evidence is low, and thus, patients who place a high value on survival must be adequately advised and counseled of risks and benefits when choosing intensive dialysis. Survival is but one among several critical outcomes that patients must weigh against their other needs, values, and preferences. Moving toward more transparent and evidence-informed decision making seems not only timely but essential.

Appendix A

Detailed Methods

We registered our protocol with PROSPERO (registration number: CRD42014005270).15 We applied the GRADE approach to systematic reviews and quality appraisal16-18 and prepared this article in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.19

Literature search. We searched MEDLINE (1966 to March 2016 including in-process and other nonindexed citations), Embase (1980 to March 2016), ISI Web of Science (1976 to March 2016, including conference abstracts), and CENTRAL. An experienced health information specialist developed the search strategies using terms to identify studies of intensive dialysis. The final search strategies (Appendix A) included search terms “hemodialysis,” “peritoneal dialysis,” “intensive,” “frequent,” and others, with index headings and search terms adapted for each database. We did not restrict our search by language, country, outcome, or journal. We also compiled citations from hand-searching bibliographies of identified articles and previous reviews, and related articles in PubMed and Google Scholar. In addition, we searched conference abstracts from 2010 to March 2016 for ongoing or completed studies. We downloaded all citations into Endnote X7 for de-duplication and then imported into DistillerSR20, an online collaborative systematic review software tool used for screening, calibration, and data extraction.

Study selection. We included all cohort studies with parallel arm control groups, comparator arm, and randomized controlled trials (RCTs) with >50% adult patients (≥18 years) comparing any form of intensive hemodialysis (HD) (>4 sessions/wk or >5.5 h/session) with any form of chronic dialysis (peritoneal dialysis, HD ≤4 sessions/wk or ≤5.5 h/session). Included studies reported at least 1 of our predefined outcomes of interest (mortality or hospitalization), and needed to include at least 10 adult patients on intensive dialysis and 10 adult patients on any other form of chronic dialysis. When multiple publications described overlapping patient cohorts, we reviewed all publications but based on our review on the most recent and comprehensive report. When both the abstract and full-text manuscript were available for the same patient cohort, we included only the full-text study. We excluded studies of hemodiafiltration, hemofiltration, continuous renal replacement therapy, acute kidney injury, and pre–post studies with no separate patient cohort as a comparator arm. We excluded letters, commentaries, editorials, and any other article with no original data. To reduce era effects, we excluded studies published before 2000.

Two reviewers (A.M. and S.L.) independently screened each citation using pretested forms. We retrieved full-text articles for any citation considered potentially relevant by either reviewer. Two reviewers (A.M. and N.M.) independently evaluated the eligibility of each full-text article using pre-piloted eligibility forms, and resolved discrepancies by consensus.

Outcomes. The 2 outcomes assessed were mortality and hospitalization, all-cause or cause-specific. Hospitalization was defined by either the admission rate or the number of days in hospital (per patient-year).

Data collection. We did not collect individual patient-level data. Two reviewers (N.M. and J.-A.M.) independently extracted study-level data from included studies using custom-made data extraction forms. Data items included study
design, methods, patient characteristics, definition of intensive dialysis and comparator group, and outcomes. For each outcome of interest, we extracted the unadjusted effect estimate, any adjusted effect estimates with factors included in the adjusted model, and methodological factors relevant to the quality appraisal. Disagreements in data collection were resolved by consensus, with involvement by a third reviewer (A.M.), if needed.

**Methodological quality appraisal.** We applied the GRADE quality appraisal criteria, which include risk of bias,\(^{21}\) indirectness,\(^{22}\) inconsistency,\(^{23}\) imprecision,\(^{24}\) and publication bias.\(^{25}\) We planned to assess publication bias through visual inspection of funnel plots. For RCTs, risk of bias was assessed using criteria proposed by the Cochrane Collaboration.\(^{26}\) For observational studies, we used the modified Newcastle-Ottawa criteria proposed by the CLARITY Group.\(^{20}\) We summarized meta-analysis and quality appraisal findings in GRADE evidence profile tables. We assessed the quality of evidence separately for each treatment comparison and outcome using 4 GRADE quality ratings (very low, low, moderate, and high). Pooled effect estimates based on randomized trials begin with a high-quality rating, and can be rated down for serious methodological limitations in any of the 5 quality domains. Pooled estimates based on observational studies begin with a low-quality rating, and can be further rated down based on the 5 quality domains, and can also be rated up for a large magnitude of effect, dose-response gradient, or antagonistic bias (when all plausible residual confounding would result in an overestimate of effect).\(^{27}\)

**Data synthesis.** We quantified interreviewer agreement using Cohen’s kappa coefficient. To reduce anticipated heterogeneity due to patient characteristics and/or study design, our a priori planned synthesis of results by groups was as follows: (1) RCT data were reported separately from observational studies; (2) short daily HD (>4 times per week) data were analyzed separately from nocturnal (>5.5 hours per session) data for conventional HD comparisons; (3) home and in-center patients were reported separately for conventional HD comparisons; (4) all intensive HD estimates were pooled together for comparisons with PD; and (5) when available, adjusted estimates from individual studies were used for pooling. We pooled risk estimates using the generic inverse variance method, and we planned to compute pooled effect estimates of randomized and observational studies separately. We used the \(I^2\) statistic to quantify the magnitude of heterogeneity. We used mean differences to pool the continuous outcomes of hospitalization days/patient-year and hospitalization rates/patient-year, and used hazard ratios to pool the dichotomous outcome of mortality. We used a random effects model to account for within- and between-study heterogeneity when there were more than 2 pooled studies, and a fixed model when there were 2 studies.\(^{28}\) All statistical analyses were conducted using Review Manager (RevMan) Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

**Appendix B**

**Sample Search Strategy**

1. Hemodialysis, Home/
2. (short daily adj2 (dialysis or hemodialysis or haemodialysis)).tw.
3. (long daily adj2 (dialysis or hemodialysis or haemodialysis)).tw.
4. (home adj2 (dialysis or hemodialysis or haemodialysis)).tw.
5. ((nocturnal or night$) adj2 (dialysis or hemodialysis or haemodialysis)).tw.
6. (intensive adj2 (dialysis or hemodialysis or haemodialysis)).tw.
7. (daily adj (haemodialysis or hemodialysis)).tw.
8. or/1-7
9. remove duplicates from 8

**Appendix C**

Risk of Bias Assessment for Studies Included in Meta-Analysis.

| Author   | Year | Q1            | Q2            | Q3            | Q4            | Q5            | Q6            | Q7            | Q8            |
|----------|------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Johansen | 2009 | Definitely yes| Definitely yes| Definitely yes| Mostly yes    | Probably yes  | Definitely yes| Definitely yes| Definitely yes|
| Lacson   | 2010 | Probably yes  | Definitely yes| Definitely yes| Mostly yes    | Probably yes  | Definitely yes| Definitely yes| Definitely yes|
| Lacson   | 2012 | Definitely yes| Definitely yes| Definitely yes| Mostly yes    | Probably yes  | Definitely yes| Definitely yes| Definitely yes|
| Nesrallah| 2012 | Probably no   | Definitely yes| Definitely yes| Mostly yes    | Probably yes  | Definitely yes| Definitely yes| Definitely yes|
| OK       | 2010 | Definitely yes| Definitely yes| Definitely yes| Mostly yes    | Probably yes  | Definitely yes| Definitely yes| Probably yes  |

(continued)
### Tool to Assess Risk of Bias in Cohort Studies

1. Was selection of exposed and nonexposed cohorts drawn from the same population?
2. Can we be confident in the assessment of exposure?
3. Can we be confident that the outcome of interest was not present at start of study?
4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?
5. Can we be confident in the assessment of the presence or absence of prognostic factors?
6. Can we be confident in the assessment of outcome?
7. Was the follow-up of cohorts adequate?
8. Were co-interventions similar between groups?

### Ethics Approval and Consent to Participate

Waived by the Northwell Health Feinstein Institute for Medical Research Institutional Review Board (IRB).

### Consent for Publication

We have the authors consent for publication.

### Availability of Data and Materials

All data available upon request.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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