Technology Assessment Program

End-stage Renal Disease in the Medicare Population: Frequency and Duration of Hemodialysis and Quality of Life Assessment

Technology Assessment
JHE51000
July14, 2020

Technology Assessment Program

Project ID: JHE51000

End-stage Renal Disease in the Medicare Population: Frequency and Duration of Hemodialysis and Quality of Life Assessment

Prepared for:
Agency for Healthcare Research and Quality
US Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. HHSA 290-2015-00006I

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This report is based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC), under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2015-00006-I). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program website at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Suggested citation: Shafi T, Wilson RF, Greer R, Zhang A, Sozio S, Tan M, Bass EB. End-stage Renal Disease in the Medicare Population: Frequency and Duration of Hemodialysis and Quality of Life Assessment. Technology Assessment Program Project ID No. JHE51000. (Prepared by the Johns Hopkins University Evidence-based Practice Center under contract number HHSA 290-2015-00006I) Rockville, MD: Agency for Healthcare Research and Quality. July 2020. Available at: http://www.ahrq.gov/research/findings/ta/index.html.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The Centers for Medicaid and Medicare Services requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: The Johns Hopkins University Evidence-based Practice Center (Contract Number: HHSA290201500006I). The report will be presented at a Centers for Medicare and Medicaid Services public meeting – Evidence Forum on a date not yet determined.

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The Johns Hopkins University Evidence-based Practice Center would like to thank Jeff Day, MD, MA for creating data visualization, and Jeanette Edelstein for copy editing.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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End-stage Renal Disease in the Medicare Population

Structured Abstract

Objective. To study effects of more frequent or longer hemodialysis on clinical outcomes, quality of life (QOL), and symptoms in end-stage renal disease (ESRD) patients.

Data sources. We searched through October 21, 2019 for studies in PubMed, Embase®, and other sources.

Methods. We focused on studies assessing the frequency or duration of hemodialysis using a comparison group and at least 6 months of followup. We defined usual care as hemodialysis three times per week with less than 4 hours per treatment, more frequent hemodialysis as four or more treatments per week, and longer hemodialysis as 4 or more hours per treatment. We considered study limitations, directness, consistency, and precision to grade strength of evidence (SOE) .We included studies assessing QOL in ESRD patients receiving dialysis and evaluated QOL tools using the COnsensus-based Standards for selection of health status Measurement Instruments (COSMIN).

Results. We found 17 studies (3 randomized controlled trials (RCTs), one non-randomized trial, and 13 observational studies) reported in 39 articles that addressed the impacts of increased frequency or duration of hemodialysis. Compared to the U.S. hemodialysis population, study populations were younger, healthier, and had a longer life expectancy. The SOE was low that more frequent hemodialysis compared to usual care: lowered mortality, the composite outcome of risk of death or increase in left ventricular (LV) mass, and risk of death or decrease in physical health; lowered LV mass and heart rate variability; and improved quality of life and patient reported symptom measures, blood pressure, and metabolic measures. The SOE was low that more frequent and longer hemodialysis compared to usual hemodialysis: improved blood pressure; and shortened time to recovery after hemodialysis; The SOE was low that vascular access complications were more frequent with either more frequent or more frequent and longer hemodialysis, compared to usual care.

We identified 125 QOL or symptom measure tools used in 165 studies. Ten tools were designed for use in, and validated in dialysis populations. Six tools were not designed for dialysis populations but were validated in that population. COSMIN assessments were good in four or more domains for the Kidney Disease Quality of Life instrument, and Pediatric Quality of Life Inventory.

Conclusions. More frequent in-center hemodialysis may improve clinical outcomes, mortality, and quality of life or patient-reported symptom measures. The trial populations were younger, healthier, and had a longer life-expectancy than the broader U.S. dialysis population, limiting applicability to patients with similar characteristics. Further research may increase our confidence in the findings.

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Main Points

- More frequent hemodialysis, compared with usual care, may be associated with improvement in total mortality, LV mass, blood pressure, and a few other clinical outcomes (low strength of evidence from one randomized controlled trial (RCT) and four observational studies).
- One RCT and five observational studies provided insufficient evidence of improvement in any of the reported outcomes when comparing longer hemodialysis compared with usual care.
- More frequent and longer hemodialysis, compared with usual care, may be associated with improvement in some clinical outcomes including blood pressure, and a few other clinical measures (low strength of evidence from one RCT, and four observational studies reporting on these outcomes).
- Compared to usual care, more frequent (one RCT) as well as more frequent and longer hemodialysis (one RCT) may be associated with higher risk of vascular access complications (low strength of evidence).
- The mortality rates in RCT and observational studies were lower than the rate in the U.S. hemodialysis population.
- Of 125 quality of life (QOL) and symptom measurement tools, 10 tools were designed to measure QOL or symptoms in patients on dialysis. Six tools were designed for a non-dialysis population but validated in populations on dialysis.
- The most commonly used tools validated in the dialysis population were the Kidney Disease Quality of Life instrument, Kidney Disease Quality of Life-36 instrument, and Short Form-36.
- Methodologic assessments of the quality of dialysis-specific tools varied from poor to good for different domains of the COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN).

Background and Purpose

Despite many advances in general medical care and standardization of dialysis care, 20-25 percent of incident dialysis patients do not survive the first year of dialysis and median survival is only 4 years.[1] Patients receiving dialysis also report poor QOL. Most patients experience uremic symptoms such as fatigue, poor appetite, malnutrition, poor sleep quality, restless legs,

sexual difficulties, frailty, and cognitive impairment.[2-4] QOL is often valued by patients even more than survival,[5-7] but it remains understudied.

Nephrologists have been interested in determining whether more frequent or longer hemodialysis treatments can improve patient outcomes.

We conducted a systematic review to determine the effects of more frequent or longer hemodialysis on clinical outcomes, QOL and symptom measures in ESRD patients. We also sought to identify evidence gaps for future research.

Methods

This technology assessment followed the methods in the Agency for Healthcare Research and Quality Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[8] The protocol is available at: https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/esrd-protocol-2019-amended.pdf

Results

Table A provides a summary of the results based on 3 RCTs, 1 non-randomized trial, and 13 observational studies (low strength of evidence). The remainder of important outcomes had insufficient evidence or were not reported. All interventions are compared with usual care (hemodialysis 3 treatments per week, less than 4 hours per treatment).

Table B provides an overview of tools used to measure QOL and symptoms in people on dialysis.

Limitations

The reported studies had limited generalizability to the U.S. Medicare hemodialysis population. The studies of more frequent hemodialysis were conducted among incenter hemodialysis whereas most patients receiving frequent hemodialysis in the U.S. are treated at home using a hemodialysis system not tested in RCTs.

Implications and Conclusions

More frequent incenter hemodialysis may improve clinical outcomes, mortality, and quality of life. The clinical trial populations studied were on average, younger, healthier, and had a longer life-expectancy than the broader U.S. hemodialysis population limiting applicability to hemodialysis patients with similar characteristics.

The strength of evidence supporting this conclusion is low meaning that further research may change our confidence in the findings.

Rigorous studies are needed to better establish the validity and reliability of the QOL and symptom instruments used in dialysis patients. Studies also are needed to establish the minimal

clinically important difference and potential placebo effect associated with each QOL or symptom instrument.

Table A. Summary of outcomes with low strength of evidence* in individuals receiving more frequent and or longer duration hemodialysis.†

Intervention	Outcomes Favoring Intervention	Outcomes Favoring Usual Care
More Frequent hemodialysis	Mortality Rate Death or increase in LV mass‡ Death or decrease in physical health‡ Number of antihypertensive medications prescribed/used Interdialytic weight gain Heart rate variability improvement Hemoglobin concentration‡ Serum phosphorous Phosphorous binder dose Bicarbonate levels RAND-36 Emotional well-being‡ RAND-36 Energy/Fatigue‡ RAND-36 General Health Scale‡ RAND-36 Mental health composite RAND-36 Physical health composite Recovery time after hemodialysis Intradialytic hypotension	Vascular access complications
More Frequent and Longer Duration hemodialysis	Number of antihypertensive medications prescribed/used Interdialytic weight gain Pre-hemodialysis change in BP Ultrafiltration rate Serum phosphorous	Bicarbonate levels Vascular access complications Loss of residual kidney function

BP = blood pressure; IE = insufficient evidence to assess strength of evidence; LV = left ventricular

*Low strength of evidence indicates that further research is likely to change our confidence in the estimate of the effect and is likely to change the effect estimate.

† The evidence was insufficient on how increased duration of hemodialysis affected any of the outcomes;

‡ Significant difference between groups

Table B. Summary of quality of life and symptom measures in tools designed and validated in an ESRD population (specific), and in tools not designed, but validated in an ESRD population (validated).*

Tool	N Studies	Reliability reported	Validity reported	MCID reported	COSMIN assessment (good/ total)‡‡
Specific: KDQOL†	30	Y	N‖	N	Y (1/7)
Specific: KDQOL-36†	33	Y	N	N	Y (3/7)
Specific: PedsQL†	6	Y	N‖	Y	Y (3/7)
Specific: DSI	8	Y	Y	N	Y (2/6)
Specific: CHEQ†	4	N‡	N	N	Y (3/7)
Specific: Home Dialysis Interview Schedule	1	N	N	N	N
Specific: KDQ	1	N	N	N	N
Specific: RQLP	1	N	Y	N	N
Specific: Unnamed validated questionnaire specifically designed for use in ESRD	1	N	N	N	N
Specific: General dialysis treatment stress scale	1	N	N	N	N
Validated: SF-36	36	N‡	N	Y††	N
Validated: BDI	23	Y	N‖	N	N
Validated: RAND-36	3	N	N	Y††	N
Validated: SF-12	4	N‡	N	N	N
Validated: HADS	3	N	N	N	N

Validated: PHQ-9	4	N	N	N	N

* Validation methods were reported for all ESRD specific and ESRD validated tools; Placebo effect was measured using the KDQ and multiple subscales of the SF-36
†Reliability and validity measures identified for overall tool and multiple subscales
‡Reliability reported for the sleep quality subscale
‖Validity measures reported for some subscales but not the overall tool
††MCID reported for some subscales
⌗ We assessed domains only if enough information was available.

BDI = Beck Depression Inventory; CHEQ = CHOICE Health Experience Questionnaire; DSI = dialysis symptom index; ESRD = end-stage renal disease; HADS = Hospital Anxiety and Depression Scale; KDQ = kidney disease quality; KDQOL = Kidney Disease Quality of Life; KDQOL-36 =Kidney Disease Quality of Life, 36; MCID = minimal clinically important difference; PedsQL = Pediatric Quality of Life; PHQ-9 = Physicians Health Questionnaire, 9; RQLP = Renal Quality of Life Profile; SF-12 = Short form 12; SF-36 = Short form 36

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Introduction

Background

In the U.S, over 100,000 patients, both children and adults, reach end-stage renal disease (ESRD) every year, and approximately 500,000 ESRD patients are on maintenance dialysis.[1] In 2014, 8,600 patients were treated with home hemodialysis.[2] The U.S.ESRD population is expanding, and recent projections suggest that by 2030 up to 1.3 million patients will be on maintenance dialysis.[3]

Hemodialysis works by replacing some of the kidney functions. It is effective in removing volume and many non-protein bound substances. The contemporary hemodialysis prescription of three times per week is based on the dialysis prescription considered minimally adequate in 1973, when the Medicare ESRD legislation was passed. This hemodialysis frequency, established by trial and error, was guided by the control of patients' uremic symptoms.[4] In the 1960s, treatments took place once weekly and lasted 20 to 24 hours per treatment. Owing to recurrent uremic symptoms, frequency was increased to twice weekly for 16 to 23 hours per treatment, and later to thrice weekly for 8 to 10 hours per treatment.[5] In 1973, the thrice weekly 8- to 10-hour treatment schedule was the norm when the Medicare ESRD legislation was passed. In subsequent decades, the focus gradually shifted to achieving optimal urea clearance on dialysis, as a marker of adequate clearance of all uremic toxins. Improvements in hemodialysis technique and technology allowed reaching the urea clearance targets in shorter periods of time, leading to the current practice of thrice weekly hemodialysis for 3 to 4 hours per treatment. The U.S. Dialysis Outcomes and Practice Patterns Study reported that the hemodialysis facility mean treatment time varied by 30 minutes (10th/90th percentiles: 204 minutes, 234 minutes).[6] Therefore 4 hours represents an extended treatment compared to the national mean.

In contemporary clinical practice, despite many advances in general medical care and standardization of dialysis care, 25 percent of incident dialysis patients do not survive the first year of dialysis. Median survival is only 4 years, and 5-year survival is about 40 percent.[1] Patients receiving dialysis also report poor quality of life (QOL) with most patients experiencing uremic symptoms such as fatigue, poor appetite, malnutrition, poor sleep quality, restless legs, sexual difficulties, frailty, and cognitive impairment.[7-9] QOL is often valued by patients even more than survival,[10-12] but it remains understudied.

Based on the knowledge that kidneys provide continuous clearance, as opposed to the intermittent clearance provided by hemodialysis, nephrologists have been interested in determining whether poor patient outcomes observed in the hemodialysis population treated with thrice weekly hemodialysis for 3 to 4 hours per treatment can by enhanced by more frequent and longer hemodialysis treatments, which may reduce fluid overload and accumulation of uremic toxins.

Decisional Dilemma Regarding the Frequency and Duration of Hemodialysis

Decisional dilemmas occur when considering the prescription of more frequent or longer hemodialysis treatments. First, the major benefit of more frequent or longer hemodialysis treatment seems to be from greater total volume removal. However, each hemodialysis treatment can be associated with potential risks, including infection, intradialytic hypotension (and its complications such as myocardial stunning), loss of residual kidney function, and infectious

events. Second, unintended decisional conflicts may result from Medicare payment policies which consider per treatment estimation of hemodialysis urea clearance (Kt/Vurea) as a quality metric rather than the original intent of hemodialysis, namely rehabilitation of uremic patients to a fully functional status. It is widely recognized in clinical practice that a person meeting all quality targets may have a very poor QOL. Thus, determination of an optimal dialysis regimen requires multimodal measures that incorporate patient reported and comprehensive clinical and dialysis-related measures.[13] Scheduling more frequent or longer hemodialysis treatments could be one of the ways to provide optimal dialysis. However, healthcare system and payor decisional conflicts arise when approval is sought for more frequent hemodialysis in patients considered "adequately" dialyzed based solely on Kt/Vurea quality metrics.[14]

Finally, patient perspective is essential to put decisions in context. Each hemodialysis treatment takes several hours away from a day and is associated with a small but finite risk of vascular access complications, blood stream infections, cramping during dialysis, and postdialysis fatigue. The inconvenience and risks might be balanced against fewer uremic symptoms, greater energy, better QOL, and the ability to maintain employment. A systematic review on the comparison between more frequent or longer hemodialysis and standard hemodialysis will help identify key issues for future studies and guide quality improvement efforts toward improving patient-centered outcomes.

We conducted a systematic review to determine the effects of more frequent or longer hemodialysis on clinical outcomes and QOL in ESRD patients. In addition to summarizing the currently available evidence, we sought to identify evidence gaps that need to be addressed in future research.

Key Questions (KQ)s and Scope of the Review

The KQs were posted for public comment between July 5 and August 17, 2019. Comments were received from federal agency officials, advocacy groups representing patients and providers, and a dialysis center. Commenters agreed that the review should include information on subgroups, include data from both randomized controlled trials (RCTs) and observational studies, and include all QOL tools that were validated in any dialysis populations.

Key Question 1

In studies of frequency and duration of hemodialysis in non-institutionalized individuals, what are the characteristics of the patients and hemodialysis modality (including home or hemodialysis center setting and flow rate)? What is the length of followup on patients in the studies? How does this compare to the general population of patients on hemodialysis?

Key Question 2

In hemodialysis patients, does more frequent hemodialysis (more than three times a week) improve objective outcomes (including hypertension control, mortality, and QOL) over the long term (more than 6 months) compared with usual hemodialysis frequency (three times a week)? What is the impact of patient characteristics and modality of hemodialysis used in the studies on outcomes?

Key Question 3

In hemodialysis patients, does extended hemodialysis duration (daytime, 4 or more hours per treatment; or nocturnal, overnight) improve objective outcomes (including hypertension control, mortality, and QOL) over the long term (more than 6 months) compared with usual length hemodialysis duration (less than 4 hours)? What is the impact of patient characteristics and modality used in the studies on outcomes?

Key Question 4

What instruments have been used to measure QOL in studies of people with ESRD treated by dialysis?

Subquestion 4a: What are the psychometric properties of instruments used to measure QOL in studies of people with ESRD treated by dialysis?

Subquestion 4b: What is the minimal clinically important difference for instruments used to measure QOL in studies of people with ESRD treated by dialysis?

Subquestion 4c: How have instruments used to measure QOL in studies of people with ESRD treated by dialysis been validated?

Subquestion 4d: What is the impact of placebo effect in studies used to measure QOL in people with ESRD treated by dialysis and what study designs are needed to mitigate the impact?

We used the PICOTS typology (Populations, Interventions, Comparators, Outcomes, Timing, and Setting) to define the scope of the review, as indicated below in Table 1. The analytic framework is shown in Figure 1.

Table 1. Scope of the review.

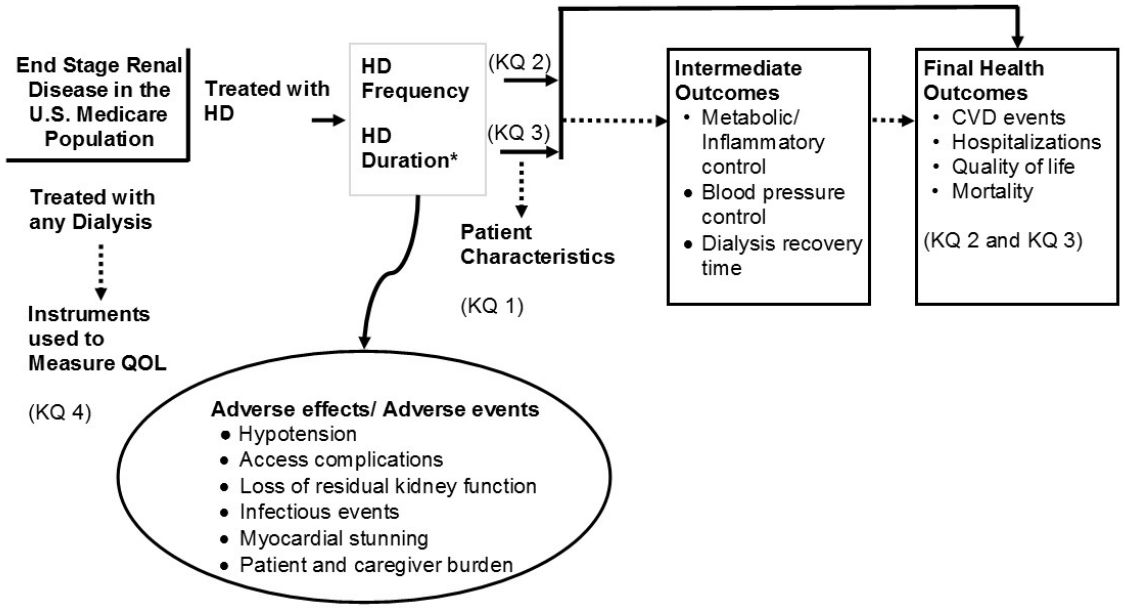
PICOT	Description
Populations	• All KQs: U.S.ESRD population (non-institutionalized) • KQ 1: Adults and children with ESRD on hemodialysis (no age restriction) • KQs 2 and 3: Adults and children with ESRD on hemodialysis • KQ 4: Adults and children with ESRD treated with any dialysis or other non-transplant treatment
Interventions	• KQ 1: Different frequency or duration of hemodialysis • KQ 2: More frequent hemodialysis (three versus > three treatments per week) • KQ 3: Increased duration of hemodialysis treatments (<12 hours versus ≥12 hours per week; or daytime versus nighttime) • KQ 4: Studies of QOL in people with ESRD receiving any type of dialysis. We sought to include data on all home hemodialysis machines (2008K@Home Hemodialysis Machines, NxStage® System One, NxStage® System S) as well as all devices used in-center.
Comparators	• KQs 1 and 4: Usual care (three times per week and 3 to <4 hours per treatment, with 9 to < 12 hours per week). • KQ 2: More frequent hemodialysis (> three treatments per week); usual care • KQ 3: Increased duration of hemodialysis treatments ≥12 hours per week, or nocturnal, overnight); usual care

PICOT	Description
Outcomes	• KQ 1: Not applicable • KQs 2 and 3: (see Appendix A for a detailed list of outcomes for these KQs) o Final health outcomes: clinical outcomes including cardiovascular events, hospitalizations, QOL, pregnancy outcomes, and mortality o Adverse events: intradialytic hypotension, access complications, loss of residual kidney function, infectious events, myocardial stunning hospitalizations, and patient and caregiver burden o Intermediate outcomes: metabolic/inflammatory control, blood pressure control, hemodialysis recovery time • KQ 4: o Instruments used to measure QOL in dialysis patients o Psychometric properties of these instruments o Minimal clinically important difference for these instruments o Validation of these instruments o Placebo effect in studies of QOL in dialysis patients and what study designs are needed to mitigate the impact
Timing	• KQs 1, 2, and 3: Minimum of 6 months of followup after the intervention is initiated • KQ 4: No minimum followup
Setting	• Home dialysis and dialysis center (non-institutionalized)

* Usual care involves 3 treatments per week with an average of 3.5 hours per treatment and a minimum of 3 hours per treatment

ESRD = end-stage renal disease; KQ = key question; QOL = quality of life

Figure 1. Analytic framework for addressing the KQs. While KQs 1-3 focus on studies of ESRD patients treated with hemodialysis, KQ 4 covers all instruments used to measure QOL in ESRD patients treated with any form of dialysis.



CVD=cardiovascular disease; HD=hemodialysis; KQ=key question; QOL=quality of life

* Treatment decision may be one-time, or varies over time.

Methods

We prepared this technology assessment following the methods outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[15] The protocol is available at: https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/esrd-protocol-2019-amended.pdf

Literature Search Strategy

Search Strategy

We searched the PubMed, Embase™, and the Cochrane Library databases for primary studies. Two comprehensive search strategies were developed: one for KQs 1, 2, and 3, and the other for KQ 4. Search strategies were developed in PubMed based on an analysis of medical subject headings (MeSH®), text words from eligible primary studies identified a priori, and with input from internal experts and the technical expert panel. The PubMed search strategy was adapted for and applied to EMBASE, and the Cochrane Library (see Appendix B). For KQs 1, 2, and 3, searches of all databases were limited to articles published between January 1, 2005 and October 21, 2019. For KQ 4, the search included any articles up until October 21, 2019 without any other date limitation. The date limitation for KQs 1, 2, and 3 is driven by the fact that, in the present era, more frequent hemodialysis is generally prescribed at home, and became feasible after the availability of the NxStage home hemodialysis machine in 2005.[2] We conducted hand searches using the reference lists of included articles and relevant reviews. Searches will be updated when the draft report is submitted for peer review.

We also conducted a grey literature search for all KQs to identify evidence that may not appear in the peer reviewed literature or is ongoing at ClinicalTrials.gov. We also searched Scopus®, using the same date restrictions used for the published literature search (January 1, 2005 to April 1, 2019). The grey literature search was intended to identify additional sources of data and help estimate potential publication bias.

KQ 4 addresses the identification of tools used to assess QOL in individuals with ESRD on any form of dialysis (hemodialysis and peritoneal dialysis). We conducted additional searches of the Patient Reported Outcomes Measurement Information System (PROMIS®) Health Measures website[16] for information on patient reported outcome measures (PROMs) that have or can be applied to the U.S.ESRD populations. The PROMIS® website provides information on the methodology used for developing its measures and, for applicable PROMs, we used this site to obtain information on psychometric properties, if available. In addition to searching the PROMIS website, we conducted additional supplemental searches to identify information to answer KQ 4 subquestions. We conducted supplemental searches on specific QOL and symptom tools to look for additional information on psychometric properties, minimal clinically important difference, and validation methods.

Inclusion and Exclusion Criteria

Our target population was U.S. ESRD patients treated with hemodialysis, including adults and children, who ordinarily would be eligible for Medicare. As more than 90% of U.S. patients reaching ESRD are eligible for Medicare, we included all studies of the U.S. ESRD population that were conducted in a home or incenter setting. We included studies reporting results from

multinational studies, if the U.S. participants constituted more than or equal to 50% of the study population or if the results were stratified by country so that the U.S. results could be abstracted.

For KQs 1, 2, and 3, we limited our literature search to 2005 and later as, in the present era, more frequent hemodialysis prescribed at home increased after the availability of the NxStage home hemodialysis machine in 2005.[2] We did not impose this limitation on KQ 4 focused on QOL instruments.

These inclusion and exclusion criteria were developed a priori before literature search and data abstraction and informed by feedback from the Technical Expert Panel. Table 2 summarizes our detailed inclusion and exclusion criteria based on the PICOTS (Population, Intervention, Comparison, Outcomes, Timing, Setting and Study design) framework.

For KQ 1, we included all study designs that include a comparison group (i.e., RCTs, non-randomized controlled trials, and prospective and retrospective cohort studies with a comparison group) on frequency or duration of hemodialysis over the long term (i.e., more than six months).

For KQ2, we included all study designs that include a comparison group (i.e., RCTs, non-randomized trials, prospective and retrospective cohort studies with a comparison group) on frequency of hemodialysis over the long term (i.e., more than six months). See Table 3 for a matrix of comparisons.

For KQ3, we included all study designs that include a comparison group (i.e., RCTs, non-randomized trials, prospective and retrospective cohort studies with a comparison group) on duration of hemodialysis over the long term (i.e., more than six months). See Table 3 for a matrix of comparisons.

KQ4 is not a comparative question and included all studies on U.S.ESRD patients receiving any form of dialysis (excluding transplant or conservative care without dialysis initiation). The main outcomes of interest can be found in Appendix B. We abstracted this information as it was presented, focusing on all QOL-related outcomes.

Studies had to include patients receiving hemodialysis to be included in KQs 1, 2, and 3. We included observational studies if they had an appropriate comparison group relevant to one of the KQs and adequate long-term followup. We excluded studies if they did not meet a minimal standard for accounting for potential confounders, including a defined control group, and adjustment for differences between groups in baseline risk factors, age, and sex. All study designs had a followup of at least six months. We compared the included observational studies to any RCTs.

Process for Study Selection

We used a three-step screening process. Owing to the large number of studies identified in the searches, we started with title screening. We used a liberal inclusion process at this level of screening. All titles were available to be screened by two screeners: one senior (i.e., a clinician or experienced methodologist), and one junior. In order for a title to be marked eligible for the next level, which was abstract screening, one or both screeners had to mark it for inclusion.

Two reviewers independently screened each study at the abstract and the full-text stage. Screeners needed to agree on inclusion or exclusion for each article. Screeners did not need to agree on the reason for exclusion. Disagreements that could not be resolved by the two reviewers were resolved by the internal experts. At random intervals during screening, senior team members conducted quality checks to ensure that inclusion/exclusion criteria were consistently applied during screening.

Table 2. Inclusion and exclusion criteria.

PICOTS	Inclusion criteria	Exclusion criteria
Population	• All KQs: U.S.ESRD population (non-institutionalized) • KQ 1: Adults and children with ESRD on hemodialysis (no age restriction) • KQs 2 and 3: Adults and children with ESRD on hemodialysis • KQ 4: Adults and children with ESRD treated with any dialysis or other non-transplant treatment.	• All KQs: non-US participants constituting more than 50% of study population • All KQs: Multinational studies if the results were not stratified by the country which prevents abstraction of U.S. results. • All KQs: hemodialysis for any indication besides ESRD (for example, acute kidney injury) • KQs 1, 2, and 3: Non-hemodialysis patients
Intervention	• KQ 1: Different frequency or duration of hemodialysis • KQ 2: More frequent hemodialysis (three versus > three treatments per week) • KQ 3: Increased duration of hemodialysis treatments (<12 hours versus ≥12 hours per week; or daytime versus nighttime) • KQ 4: Studies of QOL in people with ESRD receiving any type of dialysis.	
Comparison	• KQs 1 and 4: Usual care (three times per week and 3 to <4 hours per treatment, with 9 to < 12 hours per week). • KQ 2: More frequent hemodialysis (> three treatment per week); usual care • KQ 3: Increased duration of hemodialysis treatments (≥12 hours per week, or nocturnal, overnight); usual care • See Table 1	• Studies that did not have a comparison group for outcomes
Outcomes	• KQ 1: Not applicable • KQs 2 and 3: o Final health outcomes: clinical outcomes including mortality, cardiovascular events, hospitalizations, QOL, and pregnancy outcomes (see Appendix A) o Intermediate outcomes: metabolic/inflammatory control, blood pressure control, hemodialysis recovery time o Adverse events: intradialytic hypotension, access complications, loss of residual kidney function, infectious events, myocardial stunning hospitalizations, and patient and caregiver burden • KQ 4: o Instruments used to measure QOL in dialysis patients o Psychometric properties of these instruments o Minimal clinically important difference for these instruments o Validation of these instruments o Placebo effect in studies of QOL in dialysis patients and what study designs are needed to mitigate the impact	• NA because all outcomes are considered
Timing and setting	• KQs 1, 2, and 3: Minimum of 6 months of followup after the intervention is initiated • KQ 4: no minimum followup	• KQs 1, 2, and 3: followup of less than six months after initiation of the intervention
Setting	• Incenter or home dialysis	• Institutionalized patients

* Usual care involves 3 treatments per week with an average of 3.5 hours per treatment and a minimum of 3 hours per treatment
ESRD = end-stage renal disease; KQ = key question; NA = not applicable; QOL = Quality of life

Table 3. Duration and frequency of hemodialysis under consideration for KQs 1, 2, and 3.

		Duration (hours per treatment)	
		Less than 4 hours	4 hours or more
Frequency of treatments per week	Three treatments	9 to <12* hours per week	≥ 12 hours per week
	Four or more treatments	9 to <16** hours per week	≥ 16 hours per week

* Usual care involves 3 treatments per week with an average of 3.5 hours per treatment and a minimum of 3 hours per treatment
** The duration of each hemodialysis treatment is generally shorter when hemodialysis is done more frequently.

Data Extraction and Data Management

We used Distiller SR (Evidence Partners, Ottawa, Canada) to manage the screening and data extraction process. Distiller SR is a web-based data management program that manages all levels of the review process.[17] All applicable articles identified by the search process were uploaded to the system.

We used a systematic approach to extract the data to minimize the risk of bias or errors in this process. We created and pilot tested standardized forms for data abstraction (Appendix B). Each article underwent double review by study investigators for data abstraction. A senior level reviewer (i.e., a clinician or experienced systematic review methodologist) confirmed the first reviewer's abstraction for completeness and accuracy. A third reviewer randomly audited a sample assessed by the first two reviewers to ensure consistency in the data abstraction. Reviewers were not masked to the articles' authors, institutions, or journals. All information from the article review process was entered into a DistillerSR database by the first reviewer. We used the DistillerSR database to maintain the data and to create detailed evidence tables and summary tables (see Appendix C).

Risk of Bias Assessment

We assessed the methodological risk of bias (study limitations) in studies addressing KQs 2 and 3. The assessments of risk of bias were conducted independently and in duplicate based on the Cochrane Risk of Bias tool for randomized studies (ROB2),[18] and the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I).[19] We resolved differences between reviewers through consensus. We judged the overall risk of bias for each study based on the adjudicated ratings for the individual risk of bias items. RCTs had three overall ratings for risk of bias (low, high, and unclear) and observational studies had five overall ratings (low, moderate, serious, critical, and no information). We did not evaluate the methodological risk of bias for studies included in KQ 4 if they did not address KQ2 or KQ3.

We assessed the individual risk of bias (study limitations) for RCTs[18] using five items:

- Risk of bias arising from the randomization process;
- Risk of bias due to deviations from the intended interventions: effect of assignment to intervention, and effect of adhering to intervention;
- Risk of bias due to missing outcome data;
- Risk of bias in measurement of the outcome;
- Risk of bias in selection of the reported result.

Following the ROB2 guidance in reaching final judgements, the following considerations apply: concerns should be expressed only about issues that are likely to affect the ability to draw reliable conclusions from the study. Judgement of 'High' risk of bias for any individual domain will lead to the result being at 'High' risk of bias overall, and a judgement of 'Some concerns' for any individual domain will lead to the result being at 'Some concerns', etc.[19]

We assessed the individual risk of bias (study limitations) for cohort studies using 7 items:

- Bias due to confounding;
- Bias in selection of participants into the study;
- Bias in classification of interventions;
- Bias due to deviations from intended interventions;
- Bias due to missing data;
- Bias in measurement of outcomes;
- Bias in selection of the reported results.

Following the ROBINS guidance, judgements were made using the following algorithm: [19].

- low risk of bias: The study is judged to be at low risk of bias for all domains,
- moderate risk of bias: The study is judged to be at low or moderate risk of bias for all domains,
- serious risk of bias: The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain,
- critical risk of bias: The study is judged to be at critical risk of bias in at least one domain,
- no information: There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias (a judgement is required for this.

Data Synthesis

Key Question 1

We qualitatively summarized the data collected for this KQ. We compared characteristics of patient populations in the studies to the U.S. Medicare hemodialysis population using publicly available data from the online U.S. Renal Data System (USRDS) Renal Data Extraction and Referencing (RenDER) System.

Key Questions 2 and 3

We reviewed all primary studies, as defined by our inclusion criteria and KQs, as well as recent meta-analyses. We included observational studies that had at least 6 months of followup. RCTs were also required to have a minimum followup of 6 months. If we included data from both RCTs and observational studies, they were not pooled for analysis.[20, 21]

We decided a priori that if we had sufficient data, we would perform a de novo meta-analysis including all studies which met our inclusion criteria. We planned to address heterogeneity using subgroup analysis and meta-regression, if there were a sufficient number of studies, or describe the heterogeneity qualitatively, if there were not. We did not combine clinically or methodologically diverse studies but, rather, described the differences among the studies and population characteristics.

If studies were not too diverse clinically or methodologically, we planned to evaluate the presence of statistical heterogeneity, using tests such as Cochran's Q test and the I-squared statistic, to measure the magnitude of heterogeneity.[15, 18] The 95 percent confidence interval for the I-squared statistic was intended to reflect the uncertainty in the estimate of the magnitude of heterogeneity. Though a naïve categorization of values for I-squared would not be appropriate for all circumstances, we tentatively assigned adjectives of low, moderate, and high to I-squared values of 25 percent, 50 percent, and 75 percent, respectively. If statistical heterogeneity was attributable to one or two "outlier" studies, we planned to conduct sensitivity analyses by excluding these studies.

Key Question 4

We qualitatively presented data collected for this KQ. To address this question, we provided a list of QOL and symptom measure tools used in a dialysis population. Tools were recorded as they were reported in each included article. The SF-36 and RAND-36 were recorded as separate tools. They include the same set of questions, but the scoring algorithms are different for the pain subscale and the general health subscale.[22]

We collected and summarized information about the psychometric properties, including reliability, validity, feasibility, and usability, of tools designed for use in dialysis patients or validated for use in dialysis patients, using a format consistent with the way the properties were defined in the source materials. We also extracted any reported information about the minimal clinically important difference associated with the QOL and symptom measure tools. Validation methods for specific validity domains were described as reported in source articles, and definitions for specific validity domains are presented in a glossary at the end of this report. To estimate the placebo effect in double-blind RCTs, we used the difference-in-difference method, comparing the change in the treatment arm with the change in the placebo arm during followup.

We used the 2018 version of the COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN)[23] checklist to assess the quality of QOL or symptom assessment tools that were specifically designed for use in patients with ESRD and were used in more than one of the included studies. Two reviewers completed the checklist for each tool and then discussed the assessments. We used the two methods to estimate the overall methodological quality: the "worst counts" method to estimate the overall methodological quality in each measurement domain[24, 25]; the median assessment rating of applicable scores for each domain.

Grading the Body of Evidence for Each Key Question

KQs 2 and 3

At the completion of this review, two reviewers independently graded the strength of evidence on comparisons for key outcomes, including QOL, mortality, metabolic and inflammatory control, hypertension and blood pressure control, morbidity, and harms.

Grading Algorithm

We used the grading scheme recommended in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[26] We considered the following domains: study limitations, directness, consistency, and precision.[26]

We classified the strength of evidence pertaining to the KQs into four categories:

- High (high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect)
  - One or more RCTs
  - Low study limitations
  - Direct, consistent, and precise
- Moderate (moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of effect)
  - One or more RCTs
  - Low study limitations, or some concerns
  - Direct, consistent, and precise
- Low (low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the effect estimate)
  - One or no RCT
  - High study limitations, or some concerns
  - At least two of the following: indirect, inconsistent, or imprecise
- Insufficient (evidence is unavailable or insufficient to assess with any confidence).
  - One or no RCT
  - High study limitations for RCTs; or serious or critical study limitations for a cohort study
  - At least two of the following: indirect, inconsistent, or imprecise

KQs 1 and 4

We did not implement any strategy to grade the strength of the evidence for these KQs because of the descriptive nature of the questions.

Peer Review and Public Commentary

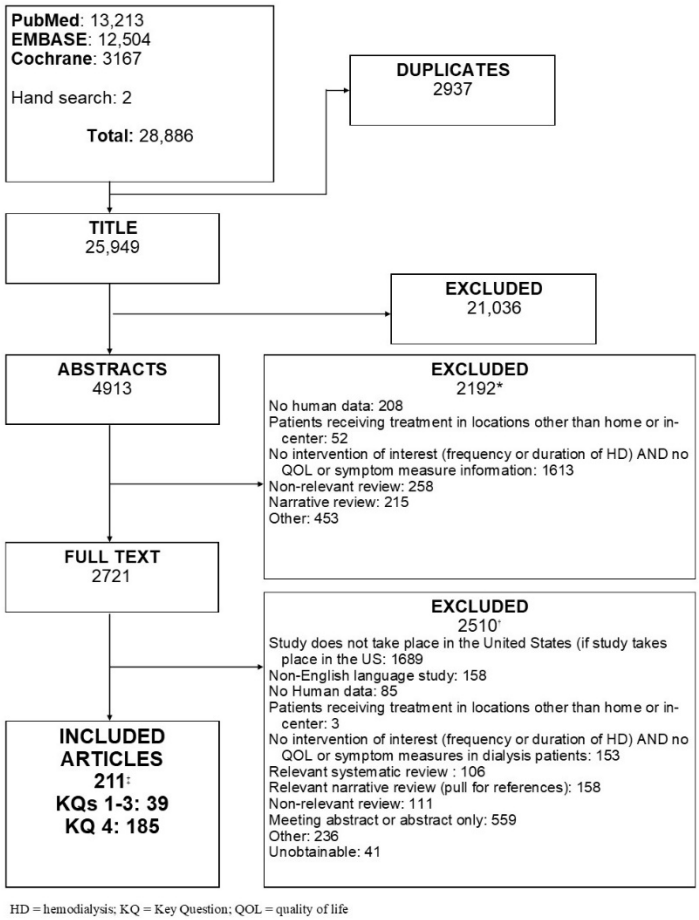
Experts in the fields of dialysis, QOL, patient-oriented research, kidney disease, and individuals representing stakeholder and user communities were invited to provide external peer review of the KQs and protocol prior to the review. AHRQ and representatives from CMS also provided comments. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We addressed reviewer comments, revising the text as appropriate, and documenting everything in a disposition of comments report that is available 3 months after the Agency posts the final systematic review on its website.

Results

Results of the Literature Search

The published literature search identified 25,949 unique citations, from which we identified 211 applicable articles (Figure 2). We identified 17 studies reported in 39 articles applicable to KQs 1, 2, and 3 (see Appendix D). We identified 165 studies reported in 185 articles applicable to KQ 4 (Figure 2). We searched Clinical Trials.gov and identified 83 potentially relevant studies. Of these, we identified 10 studying the comparison of increased duration and/or frequency of hemodialysis compared to usual care (as defined in the methods). There were no results available for these studies. Our search of Scopus returned 216 potentially eligible studies, none of which were ultimately eligible for this report.

Figure 2. Results of the literature Search



HD = hemodialysis; KQ = Key Question; QOL = quality of life

* Sum of excluded abstracts exceeds 2192 because reviewers were not required to agree on reasons for exclusion.
† Sum of excluded articles exceeds 2510 because reviewers were not required to agree on reasons for exclusion
‡ Sum of the KQ 1-3 and KQ 4 included studies exceeds 211 because 13 articles are applicable to KQ 4 and KQ 2 or 3

Key Question 1

In studies of frequency and duration of hemodialysis in non-institutionalized individuals, what are the characteristics of the patients and hemodialysis modality (including home or hemodialysis center setting and flow rate)? What is the length of followup on patients in the studies? How does this compare to the general population of patients on hemodialysis?

Key Findings

- Three RCTs (reported in 23 articles), one non-randomized trial (reported in two articles), and 13 observational studies (reported in 14 articles) reported the effects of higher hemodialysis frequencies and/or longer duration hemodialysis on outcomes.
- The mean duration of followup ranged from 1.0 to 1.7 years for RCTs, 1 to 4 years for non-randomized controlled trials, and 8.3 months to 5 years for observational studies.
- In one of the three RCTs and five of the 13 observational studies, higher frequency and/or longer duration hemodialysis took place at home. To put this in context, only 2 percent of all prevalent hemodialysis patients in the U.S. were undergoing hemodialysis at home in 2016.
- Patients included in all the RCTs and most of the observational studies were younger, but racial composition is comparable with the overall U.S. hemodialysis population.
- The mortality rate in the RCTs and observational studies was lower than in the U.S. hemodialysis population (Figure 3).

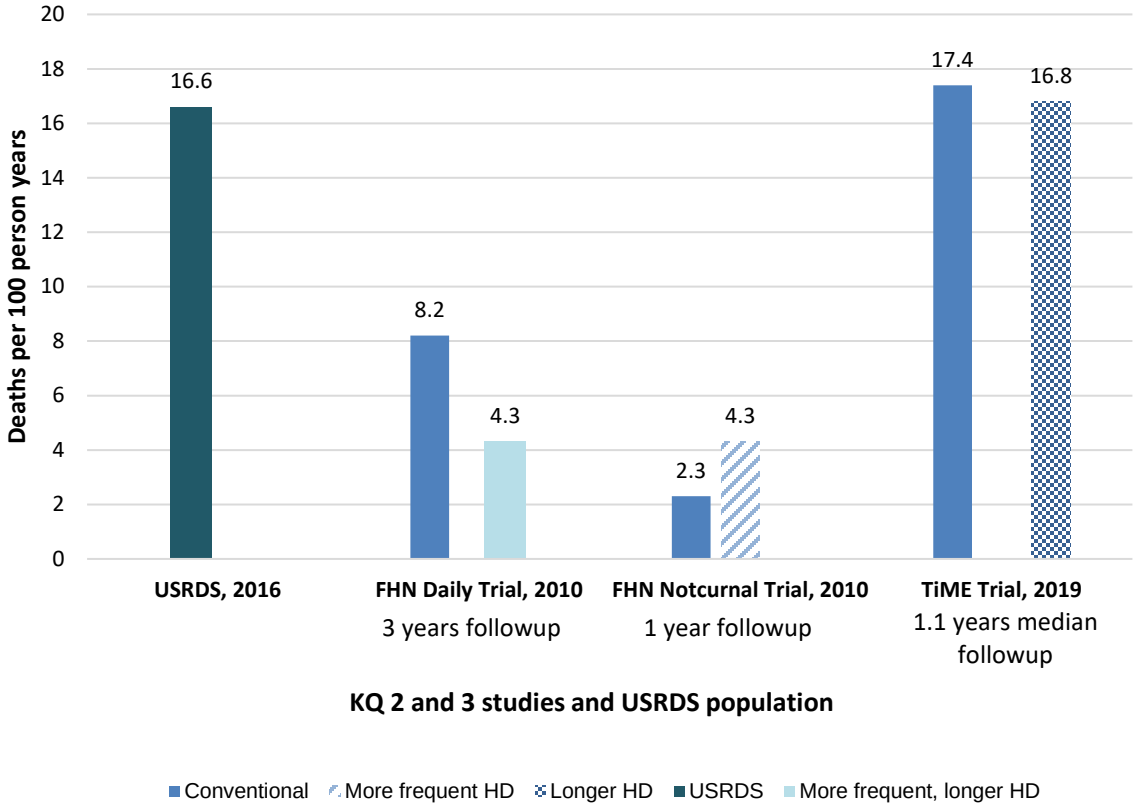
To answer the first two parts of KQ 1, we identified 17 relevant studies reported in 39 articles (Figure 4). The three RCTs were the FHN Daily trial,[27] FHN Nocturnal trial,[28] and the Time to Reduce Mortality in End-Stage Renal Disease Trial (TiME).[29] One non-randomized controlled trial[30, 31] was identified, along with 13 observational studies.[32-45]

To address the third part of KQ 1, we obtained data from the USRDS, a national data system that collects and reports information on ESRD patients in the U.S.[46] Using the online United States Renal Data System (USRDS) Query System, we assembled demographic data on the general hemodialysis population, totaling 563,634 patients.[47] Using the most recent available data year (2016), we gathered information on gender, age, race, and smoking history (Table 4).

Randomized and Non-randomized Controlled Trials

We identified three RCTs[27-29] reported in 23 articles and one non-randomized controlled trial[30, 31]reported in two articles that investigated hemodialysis frequency and duration in ESRD patients treated with hemodialysis. The full sample size of the RCTs ranged from 87 to 7,035 participants, while the non-randomized controlled trial had a sample size of 77 participants. The followup time for RCTs ranged from 1 to 1.7 years, with the non-randomized controlled trial having a followup time of up to 48 months (Table 5).

Figure 3. Mortality rates in trials of more frequent and longer hemodialysis compared to the national mortality rate for the U.S. Medicare population receiving hemodialysis.

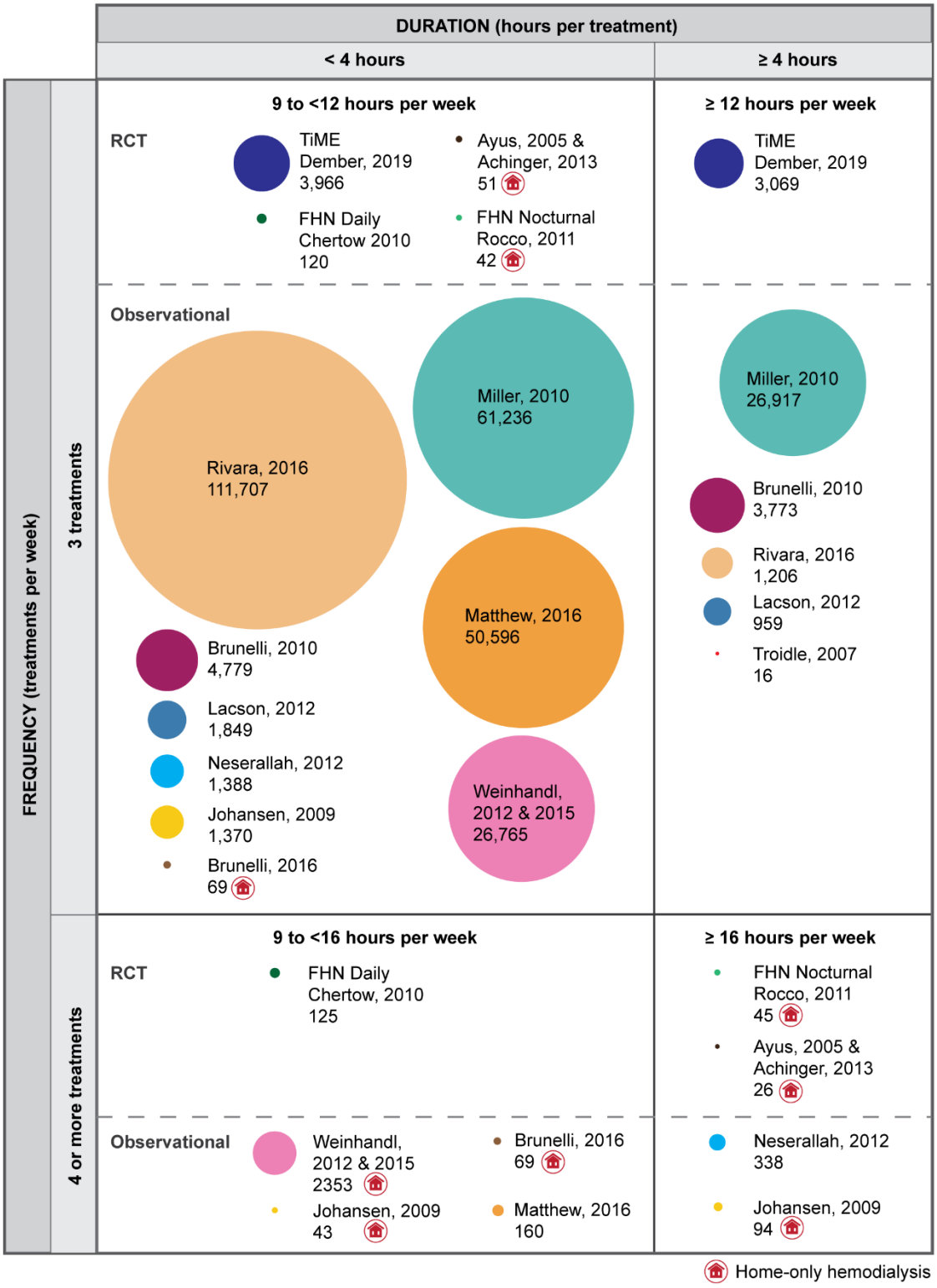


FHN = Frequent Hemodialysis Network; TiME = Time to Reduce Mortality in End-Stage Renal Disease Trial; USRDS=United States Renal Data System

*USRDS mortality rate includes both incident and prevalent ESRD patients

Note: The FHN trials were not designed or powered for mortality. The 3-year followup period includes 1 year of intervention phase and 2 years of observational followup during which time many participants returned to usual care.

Figure 4. Included studies examining more frequent, longer duration, or both of hemodialysis in people with end-stage renal disease.*



*The size of the circles illustrates the relative differences in study sample sizes for the intervention and control groups. Text with each circle is the name of the study (if available), first author, year, and sample size of the group.

Table 4. Demographic characteristics of hemodialysis patients in the U.S.in 2016, from the USRDS (N = 563,634).

Women, %	Age	Race, %	Education, %	Smoking, %
42.5	See Figure 4	White: 58.8 Black: 34.1 Latino: NR Asian/PI: 5.7 Native American: 1.0 Other: 0.3 Unknown: NR	NA	Never smoked: 53.6 Formerly smoked: 36.3 Current smokers: 10.1

NA = not available; USRDS = United States Renal Data System; NR = not reported

Table 5. Summary of the characteristics of participants in randomized and non-randomized controlled trials on the frequency or duration of hemodialysis.*

Author, year	Study name (Years of Study) Study design Followup	Location	Sample size, N (n for frequent and/or longer group)	Women, (%)	Mean age in years, overall	Race, %
Achinger, 2013[31] Ayus, 2005[30]	NR (2003-NR) Non-randomized trial 48 months	In-center Multicenter (Dialysis West, Texas Diabetes Institute)	77 (26)	33.8	51	White: 1.4 Black: 5.3 Latino: 92 Asian/PI: NR Native American: NR Other: 1.3 Unknown: NR
Chertow, 2010[27]	FHN-Daily (2006-2010) Non-blinded RCT 12 months	In-center Multicenter (multiple LDOs and single sites)	245 (125)	38.4	50.5	White: 36.3 Black: 41.7 Latino: NR Asian/PI: 8.2 Native American: 3.3 Other: 10.6 Unknown: NR
Rocco, 2011[28]	FHN-Nocturnal (2006-2010) Non-blinded RCT 12 months	Home Multicenter (multiple LDOs and single sites)	87 (45)	34.5	52.8	White: 55.2 Black: 26.4 Latino: NR Asian/PI: 14.9 Native American: 3.4 Other: NR Unknown: NR
Dember, 2019[29]	TiME (2013-2015) Pragmatic RCT Followup: Median 1.1 (IQR 0.5-1.7) years	In-center Multicenter (DaVita; Fresenius)	7035 (3069)	42.2	64.1	White: 57.8 Black: 24.8 Latino: 11.8 Asian/PI: 3.1 Native American: NR Other: 1.6 Unknown: 1.1

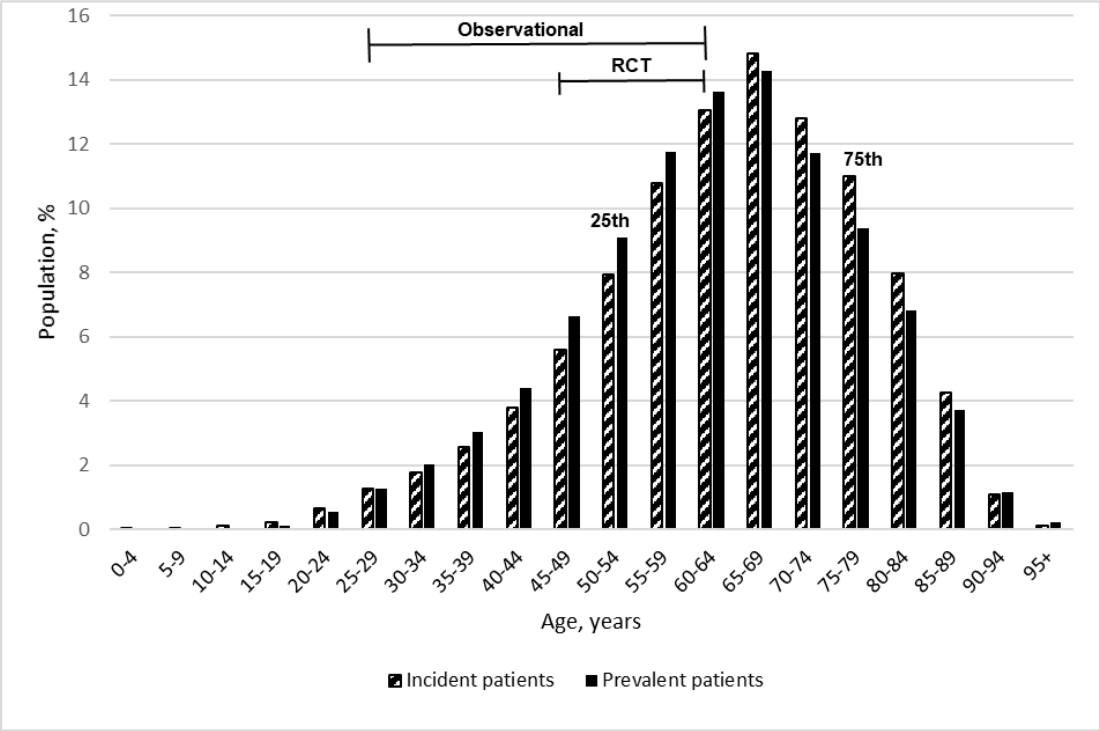
* Education and smoking history not reported.

FHN = Frequent Hemodialysis Network; N = number of patients; NA = not available; NR = not reported; PI = Pacific Islander; RCT = randomized controlled trial; TiME = Time to Reduce Mortality in End-Stage Renal Disease Trial

All three RCTs[27-29] and the non-randomized controlled trial[30, 31] were multicenter. Dialysis in two of the RCTs[27, 29] took place in-center, while one RCT took place in-home only.[28] The non-randomized controlled trial[30, 31] included patients undergoing hemodialysis incenter (Table 5). As reported by the USRDS, in 2016, 99 percent of all incident hemodialysis patients and 98 percent of all prevalent hemodialysis patients were treated by incenter hemodialysis.[48]

The mean age of patients included in the RCTs ranged from 48.9 to 64.1 years, while the mean age of patients included in the non-randomized controlled trial[30, 31] ranged from 51 to 54 years (Table 5). The age distribution in the USRDS data shows that 51.4 percent of patients were between 55 to 74 years of age, with the highest percentage of patients (14.4%) between 65 to 69 years of age (Figure 5).[47] In the RCTs, the mean percentage of female patients was 41.3 percent (with a range of 34.5% to 42.2%) and, in the non-randomized controlled trial, the mean percentage of female patients was 33.8 percent (see Table 5). In comparison to our review findings, the USRDS reported that 42.5 percent of hemodialysis patients were female in 2016 (see Table 4).[47]

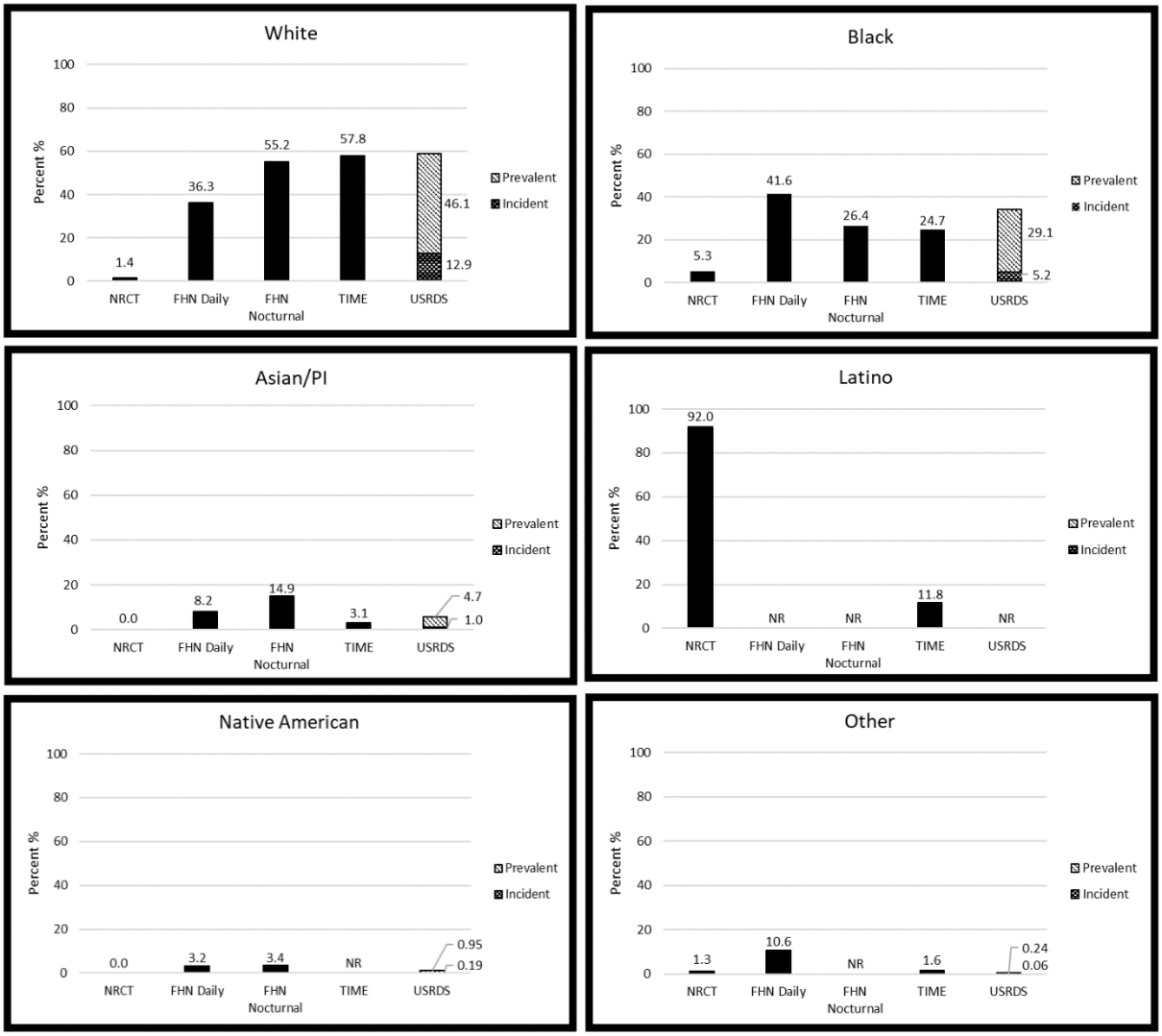
Figure 5. Mean age distribution of hemodialysis patients in the U.S. in 2016, from the USRDS.



USRDS = United States Renal Data System

Figure 6 displays the distribution of race among the trials in comparison with the USRDS data. In comparison to the percentage of White patients in the USRDS population (58.8%),[47] two of the RCTs (FHN Nocturnal and TiME)[28, 29] reported a higher percentage (55.2% and 57.8%, respectively) while the FHN Daily trial reported a lower percentage (36.3%).[27] The percentage of participants who were Black ranged from 24.7 percent to 41.6 percent among RCTs,[27-29] and was 5.3 percent in the non-randomized controlled trial.[30, 31] The USRDS reported that 34.1 percent of hemodialysis patients were Black in the 2016 cohort.[47] There was a more varied range of Asian

Figure 6. Race/ethnicity of participants in randomized and non-randomized controlled trials of hemodialysis frequency or duration, compared with 2016 USRDS data.



FHN = Frequent Hemodialysis Network; PI = Pacific Islander; NRCT = non-randomized controlled trial; TiME = Time to Reduce Mortality in End-Stage Renal Disease Trial; USRDS = United States Renal Data System

and Pacific Islander participants in the RCTs (3.1% to 14.9%)[27-29] in comparison to the USRDS (5.7%).[47] No Asian and Pacific Islanders were reported in the non-randomized controlled trial.[30] The non-randomized controlled trial reported that 92 percent of participants were Latino,[30, 31] much higher than the TiME trial (11.8%)[29], which was not reported as a separate category in the USRDS data.[47] From our literature search, only the FHN trials reported that Native Americans were included (3.2% and 3.4%). The FHN Daily trial had the largest proportion of participants with a designation of "Other" race (10.6%) (Table 5).[27]

Only the non-randomized controlled trial reported on smoking history, and only on participants who had ever smoked (44.1%) (Table 5).[30] The USRDS reported that 36.3 percent were former smokers, and 10.1 percent were current smokers (Table 5).[47] None of the trials reported on the education level of participants.

Observational Studies

Thirteen observational studies investigated hemodialysis frequency or duration in ESRD patients treated with hemodialysis, reported in 14 articles. All studies reported followup time, which ranged from a minimum of 8.3 months to a maximum of 5 years.[32-45].

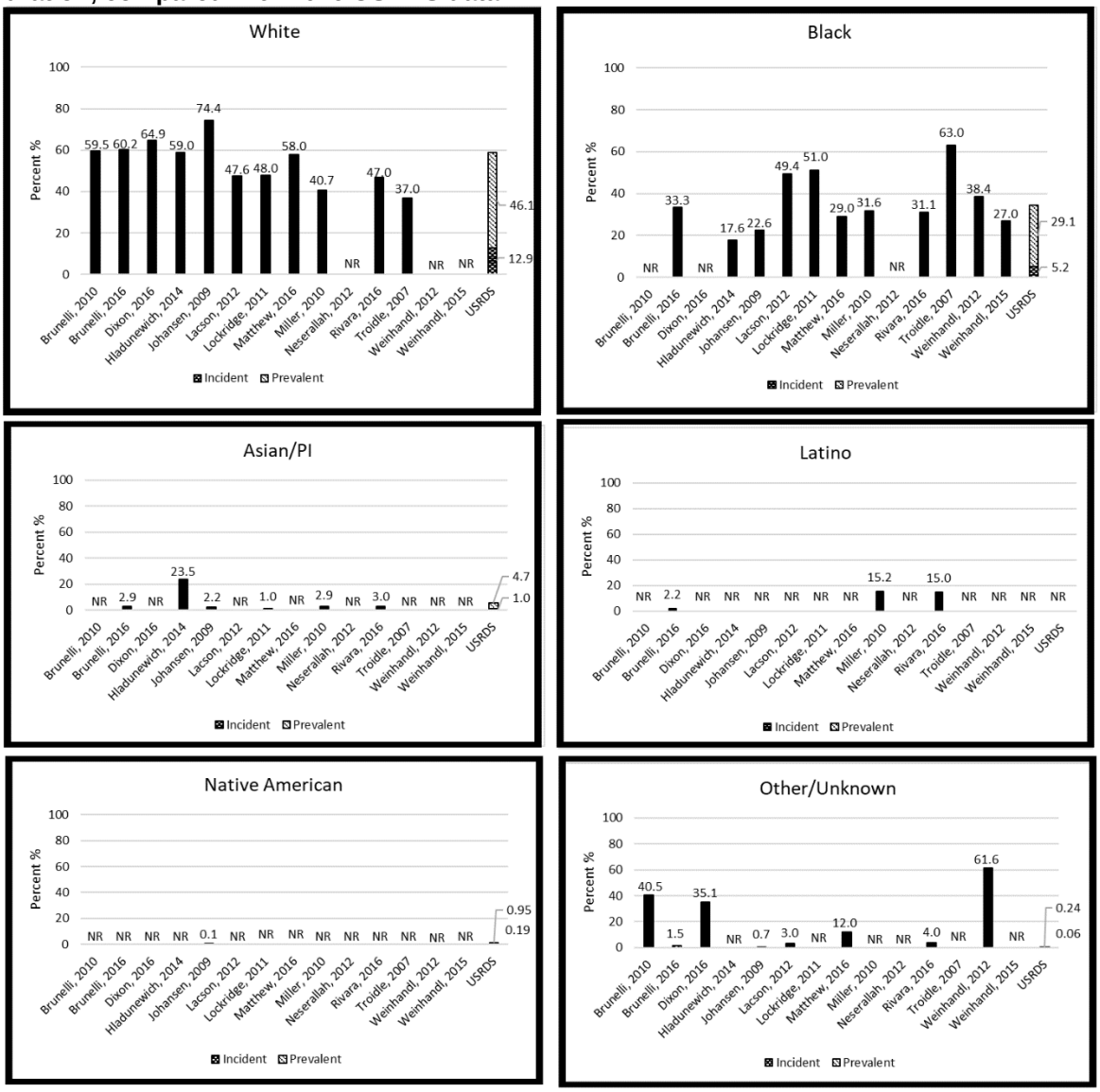
The full study size data were available for twelve of the 13 studies and ranged from 16 to 273,487 patients with a median of 50,756 patients.[32, 33, 35, 36, 38-45] The two remaining studies reported intervention arm numbers of 17 and 87 patients, with control groups from databases of unreported size.[34, 37] Prospective studies were considerably smaller in size than retrospective studies (with a range of 16 to 8,552,[36, 39, 42, 43] compared with a range of 43 to 273,487, [32-35, 37, 38, 40, 41, 44, 45], respectively). Eight of 13 studies were multicenter,[32, 35-37, 39-41, 43] and two studies occurred in single-center networks.[33, 34] One study described a multicenter network,[42] and two studies exclusively used registry data.[38, 44, 45] Eight of the 13 studies involved incenter hemodialysis exclusively.[32, 36, 40-43] Two studies used home hemodialysis,[33, 37] and four studies included data from both home and incenter hemodialysis modalities.[35, 38, 39, 44, 45] One study did not describe the hemodialysis modality.[34] None of the studies reported dialysate flow rate.

The mean age of patients in study arms ranged from 34 to 64 years.[32-39, 41, 42, 43 , 44] These mean ages reflect a younger population than the USRDS population, whose middle fifty percent (25th to 75th percentiles) of age data ranges from 54 to 72 years (Figure 4).[47] A notable difference between this literature review and the USRDS data is that USRDS includes institutionalized patients, who were not included in the reviewed studies.[47] Although only five studies excluded study patients under 18 years of age,[32, 33, 35, 40, 43] the remaining nine studies did not describe patients younger than 18 years of age in their demographics.[34, 36-39, 41, 42, 44, 45]

Except for one study arm that used a database for its control group,[37] all studies reported the distribution of men and women.[32-36, 38-45] The percentage of study participants who were women ranged from 12 percent to 100 percent, with most studies reporting between 30 percent and 48.4 percent.[32-45] This range is comparable to the 2016 USRDS population, in which 42.5 percent of hemodialysis patients were women.[47]

Collection of race demographics varied across studies (Figure 7). With the exception of two study arms,[41, 42] Percentage of white patients in the studies ranged from 37% to 76.6%, compared with the USRDS population of 58.8 percent.[32-34, 36, 37, 39-45]. The percentage of Black patients varied more widely among study arms, from 17.6 percent to 63 percent, compared with the percentage of Black patients in the USRDS population (34.1%).[32-34, 36-42, 47] With the exception of one study in which 23.5 percent of patients were Asian/Pacific Islander,[34]

Figure 7. Race/ethnicity of patients in observational studies of hemodialysis frequency or duration, compared with 2016 USRDS data.



NR = not reported; PI = Pacific Islander; USRDS = United States Renal Data System

studies underrepresented the Asian/Pacific Islander population (with a range of 0% to 7%, compared with 5.7% in the USRDS population[32, 33, 37, 40, 41, 47] Three studies reported on the Latino population, which had consistently lower representation (1.4% to 15.2%).[33, 40, 41] The Native American population was reported on in one study (0% to 3%),[45] Native Americans represent 1.1 percent of the USRDS population (Table 6).

Education and smoking characteristics were only reported in one study.[39] Among this study's arms, the percentage of those whose highest educational attainment was high school or less ranged from 29 percent to 50 percent.[39] Those who had some college education ranged among study arms from 26 percent to 44 percent, and those with a bachelor's degree varied from 6 percent to 39 percent.[39] Dixon et al. (2016) reported that most of the patients in their study arms had never smoked (55% to 61%), while smaller percentages were former smokers (23% to 36%) or current smokers (7% to 23%).[39] Data regarding education level and smoking are not available among ESRD patients from USRDS, as this information is not collected at the time of hemodialysis initiation.[47, 49]

Only two studies reported on a subgroup of their ESRD non-institutionalized hemodialysis population.[34, 39] Hladunewich et al., 2014 described pregnancy in the ESRD population, which was shown to include a younger demographic group (mean age of 34 years in the intervention group; no mean age in the control group) and focused on pregnancy outcomes associated with increased frequency and duration of hemodialysis.[34] This group was not compared with non-pregnant patients on hemodialysis. Dixon et al., 2016 included a comparison group with patients who had received a kidney transplant. These patients were more educated and had a lower rate of smoking than other arms (29% compared with 48-50% with a high school diploma or less; 7% compared with 11-23% of current smokers).[34]

Table 6. Summary of characteristics of patients in observational studies of hemodialysis frequency or duration.*

Author, year	Study name (Years of Study) Study design Followup	Location (Dialysis Provider)	Sample size, N (n for frequent and/or longer group)	Women %†	Mean age in years†	Race, %†
Brunelli, 2010[43]	ArMORR cohort (2004-2005) Observational: prospective 1 year	In-center Multicenter (Fresenius)	8,552 (3773)	45.2	62.3	White: 59.5 Non-white: 40.5
Brunelli, 2016[33]	NR (2009-2010) Observational: retrospective 1 year	Home Multicenter (DaVita)	138 (69)	30.4	**Arm1:** 57.0 **Arm2:** 57.3	White: 60.2 Black: 33.3 Latino: 2.2 Asian/PI: 2.9 Native American: NR Other/unknown: 1.5
Dixon, 2016[39]	NR (NR) Observational: prospective Mean 12 months	Home Multicenter	49‡ (18: 11/18 from FHN Nocturnal trial)	37.7	**Arm1:** 49.5 **Arm2:** 47.9 **Arm3:** 49.9	White: 64.9 Black: NR Latino: NR Asian/PI: NR Native American: NR Other/unknown: 35.1
Hladunewich, 2014[34]	NR (1990-2011) Observational: retrospective 8.3 months	Canada (Home) US (not described) Multicenter	**Toronto PreKid:** 22 pregnancies in 17 patients **US ARPD Cohort:** 70 pregnancies in 70 patients	100	**Toronto PreKid:** 34; Range: 25 to 39 **US ARPD Cohort:** 27	White: 59 Black: 17.6 Latino: NR Asian/PI: 23.5 Native American: NR Other/unknown: NR
Johansen, 2009[45]	NR (1997-2006) Observational retrospective 60 days minimum	Home (intervention) In-center (control/usual care)	1507 (137)	27.9 to 35.1	NR	White: 74.4 Black: 22.6 Asian: 2.2 Native American: 0.1 Other/unknown: 0.7

Author, year	Study name (Years of Study) Study design Followup	Location (Dialysis Provider)	Sample size, N (n for frequent and/or longer group)	Women %†	Mean age in years†	Race, %†
Lacson, 2012[36]	NR (2006-2007) Observational: prospective 2 years	In-center Multicenter (Fresenius)	2808 (959)	33.7	**Arm1:** 54.1 **Arm2:** 52.8	White: 47.62 Black: 49.38 Latino: NR Asian/PI: NR Native American: NR Other/unknown: 2.99
Lockridge, 2011[37]	NR (1997-2009) Observational: retrospective Mean 3.3 years	Home Single center	**USRDS:** NR **NHHD:** 87	**USRDS**: NR **NHHD:** 41	**Arm1:** 62 **Arm2:** 52	White: 48 Black: 51 Latino: 0 Asian/PI: 1 Native American: NR Other/unknown: NR
Mathew, 2016[32]	NR (2007-2011) Observational: retrospective 4 years	In-center Multicenter (DaVita)	50,756 (160)	35	**Arm1:** 63 **Arm2:** 62 **Arm3:** 64	White: 58 Black: 29 Latino: NR Asian/PI: NR Native American: NR Other/unknown: 11.99
Miller, 2010[41]	NR (2001-2006) Observational: retrospective 5 years	In-center Multicenter (DaVita)	88,153 (26,917)	45	61.8	White: 40.7 Black: 31.6 Latino: 15.2 Asian/PI: 2.9 Native American: NR Other/unknown: NR
Nesrallah, 2012[35]	NR (2000-2010) Observational: retrospective Median 1.8 years	In-center Multicenter	1726 (338)	48.4	Median: 52	NR
Rivara, 2016[40]	NR (2007-2011) Observational: retrospective 5 years	In-center Multicenter (DaVita)	112,913 (1206)	42.9	NR	White: 47 Black: 31.1 Latino: 15.0 Asian/PI: 3 Native American: NR Other/unknown: 4

Author, year	Study name (Years of Study) Study design Followup	Location (Dialysis Provider)	Sample size, N (n for frequent and/or longer group)	Women %†	Mean age in years†	Race, %†
Troidle, 2007[42]	NR (2005-NR) Observational: prospective Mean 10 months	In-center Single center	16 (16)	12	51.5	White: 37 Black: 63 Latino: NR Asian/PI: NR Native American: NR Other/unknown: NR
Weinhandl, 2012[38]	NR (2005-2008) Observational: retrospective Mean 1.7 to 1.8 years	Home‖ (comparison: in-center National registry data (NxStage and USRDS)	273,487 (1873)	45.0	**Arm1:** 53.2 **Arm2:** 52.2 **Arm3:** 62.6	White: NR Black: 38.4 Latino: NR Asian/PI: NR Native American: NR Other/unknown: 61.64
Weinhandl, 2015[44] (same study as Weinhandl, 2012[38])	NR (2006-2009) Observational retrospective	Home (NxStage cohort) Incenter (USRDS)	20,880 (3480)	34.4 to 34.7	53.4 to 53.6	Black: 26.8 to 27 Non-black: 73 to 73.2

ArMORR = Accelerated Mortality on Renal Replacement cohort; ARPD = American Registry for Pregnancy in Dialysis Patients; FHN = Frequent Hemodialysis Network; N = number of patients; NHHD = nocturnal home hemodialysis; NR = not reported; PI = Pacific Islander; USRDS = United States Renal Data System

*Education and smoking not reported

†Intervention arm

‡ 28 were transplant patients.

‖Daily home hemodialysis 5 to 6 days per week.

Key Question 2

In hemodialysis patients, does more frequent hemodialysis (more than three times a week) improve objective outcomes (including hypertension control, mortality, and QOL) over the long term (more than 6 months) compared with usual hemodialysis frequency (three times a week)? What is the impact of patient characteristics and modality of hemodialysis used in the studies on outcomes?

Key Findings

- One RCT and four observational studies reported the effects of more frequent hemodialysis on outcomes.
- Patients included in the RCT were less likely to be white, while most of the observational studies were comparable in the percentage of white participants to the overall U.S. hemodialysis population. Both RCT and observational studies had a younger population than the overall U.S. hemodialysis population.
- The strength of evidence was low that more frequent hemodialysis, compared with usual care, may be associated with:
  - Lower risk of death, composite outcome of death or increase in left ventricular (LV) mass, and composite outcome of death or decrease in physical health composite score;
  - Lowering of LV mass and improved heart rate variability;
  - Improvement in patient reported outcomes including general health, physical health, mental health, emotional well-being, energy/fatigue, and shorter time to recovery after completing hemodialysis treatment;
  - Improvements in a number blood pressure related parameters, including lower pre-hemodialysis systolic blood pressure, lower interdialytic weight gain, lower ultrafiltration rate, less intradialytic hypotension, and lower antihypertensive medication use;
  - Lower levels of pre-hemodialysis serum phosphorus, lower phosphorus binder dose, and higher levels of pre-hemodialysis serum bicarbonate and hemoglobin;
  - More vascular access complications.
- The evidence was insufficient to determine whether more frequent hemodialysis, compared with usual care, was associated with a difference in cardiovascular mortality.

The previous section described characteristics of patients included in studies of frequency or duration of hemodialysis (KQ 1). The following section addresses whether hemodialysis that is more frequent (more than three times per week) but of the same weekly duration improved outcomes compared with usual care (thrice weekly).

Description of Included Studies

Five studies compared the effects of more frequent hemodialysis compared with usual care, including one RCT and four observational studies. The studies were published between 2009 and 2019. The study characteristics are presented in Table 7 and Table 8.

Table 7. Summary of characteristics of randomized and non-randomized trials of the frequency of hemodialysis.

Author, year	Study name Study design	N patients (n in treatment arm) Recruitment period	Number of study centers Dialysis location	Comparison
Chertow, 2010*[27, 50-67]	FHN-Daily RCT	245 (125) 2006 to 2009	Multicenter (multiple LDOs and single sites) In-center	Frequency: three treatments per week Duration: 2.5 to 4.0 hours per treatment Frequency: six treatments per week Duration: 1.5 to 2.75 hours per treatment

FHN = Frequent Hemodialysis Network; LDO = large dialysis organization; RCT = randomized controlled trial;
*This is the main study article. Subsequent articles are cited.

Table 8. Summary of characteristics of observational studies of the frequency of hemodialysis.

Author, year	Study name Study design	N patients (n in treatment arm) Recruitment period	Number of study centers Dialysis location	Comparison
Brunelli, 2016[33]	NR Retrospective	138 (69) 2009 to 2010	DaVita Home	Frequency: five or more treatments per week Duration: 14.4 (13.3-15.5) hours per week, 3.0 (2.7-3.2) hours per treatment Frequency: three treatments per week Duration: 13.9 (12.8-15.0) hours per week, 4.1 (3.8-4.4) hours per treatment
Johansen, 2009[45]	NR Retrospective	473 (43) 1997-2006	NR Home (intervention) In-center (USRDS database)	Frequency: three treatments per week Duration: 3.5 hours per treatment Frequency: 5-6 sessions (days) per week Duration: 2.9 hours per treatment
Mathew, 2016[32]	NR Retrospective	50756 (160) 2007 to 2011	DaVita Dialysis center	Frequency: three treatments per week Frequency: two or more treatments per week Frequency: four or more treatments per week
Weinhandl, 2012[38] Weinhandl, 2015[44]	NR Retrospective	26,765 (2353) 2005 to 2009	National registry data (NxStage and USRDS) Home and Dialysis center	Frequency: Daily-Home: five or six treatments per week Frequency: Matched in-center: Three times per week in-center Frequency: All in-center: Three times per week in-center

LDO = Large dialysis organization; NR = not reported; USRDS = United States Renal Data System

The single RCT was the FHN Daily Trial.[27] The findings of the FHN Daily Trial were reported in 19 publications between 2010 and 2019. The FHN Daily Trial recruited participants between 2006 and 2009 from 11 university-based and 54 community-based hemodialysis facilities in the U.S. and Canada. The study enrolled 378 participants, of which 245 were randomized. The number of screened patients was not reported. The followup time was 12 months for the initial RCT followed by an extended observational followup period for a median of 3.6 years.[66] Four retrospective cohort studies (reported in 5 publications between 2012 and 2016)[32, 33, 38, 44, 45] compared the effects of more frequent hemodialysis with the effects of usual hemodialysis frequency. These studies included 138 to 50,322 participants in the frequent hemodialysis and usual care groups. Followup times ranged from 12 to 48 months (Table 7).

The interventions varied across studies. The FHN Daily Trial randomized participants to incenter hemodialysis six times per week with a treatment length of 1.5 to 2.75 hours (n=125) or incenter hemodialysis three times per week with a treatment length of 2.5 to 4.0 hours (n=120) for 12 months. Patients' adherence to the prescribed treatment regimen, defined as attending at least 80 percent of prescribed hemodialysis treatments, was lower in the frequent hemodialysis group than the usual care group (78% vs. 95%, respectively). The average hemodialysis frequency in the frequent hemodialysis group was 5.2 treatments per week compared with 2.88 treatments per week in the control group (Table 7). Detailed information regarding hemodialysis treatment frequency was not collected after completion of the 12-month intervention period.

The observational studies analyzed different methods and locations for administering more frequent hemodialysis. One study reported in two articles compared daily home hemodialysis patients (5 to 6 treatments per week), identified from a registry of NxStage System One users, with a matched cohort (1:5 ratio) of patients receiving thrice-weekly, incenter hemodialysis, selected from a prevalent population in the USRDS between 2005 and 2007 in one study and 2006 to 2009 in another.[38, 44]Another study compared patients receiving short daily hemodialysis (5 to 6 treatments per week) to USRDS data on usual care hemodialysis patients, collecting data from 1997 to 2006.[45] Another study used electronic health record data from a large dialysis organization to compare incident hemodialysis patients receiving incenter hemodialysis between 2007 and 2011 with different initial hemodialysis treatment frequencies (4 or more times per week, 3 times per week, or 2 or fewer time per week).[32] The treatment frequency was determined based on the hemodialysis prescription for months 4 to 6 of hemodialysis treatment. Another study compared home hemodialysis patients receiving different treatment frequencies from 2009 to 2010 from two different home hemodialysis systems (Fresenius 2008K@home patients receiving 3 or more treatments per week vs. NxStage System One patients receiving 5 or more treatments per week).[33] The treatment frequency was based on the mean number of treatments per week observed during the first 3 months of the study period, because the prescribed treatment frequency was not available. These observational studies did not report on the duration of hemodialysis treatments or the indications for receiving more frequent hemodialysis (Table 8). Information was not available on factors that contributed to patients' selection of home hemodialysis.

The study populations were heterogeneous. The FHN Daily Trial included participants from the U.S. and Canada.[27] The observational studies all included U.S. participants.[32, 33, 38, 44, 45] The proportion of females ranged from 30 percent to 38 percent and the proportion of Black patients ranged 28 percent to 42 percent. The RCT had some concerns for risk of bias,[27] two observational studies[33, 38, 44] had serious risk of bias, and two observational studies had critical risk of bias[32, 45](Table 8) (see Appendix E, Evidence Tables 1 through 4).

We were not able to conduct a meta-analysis due to the heterogeneity in study design, study populations, and outcome assessments. We synthesized the study results below, including direction and magnitude of associations.

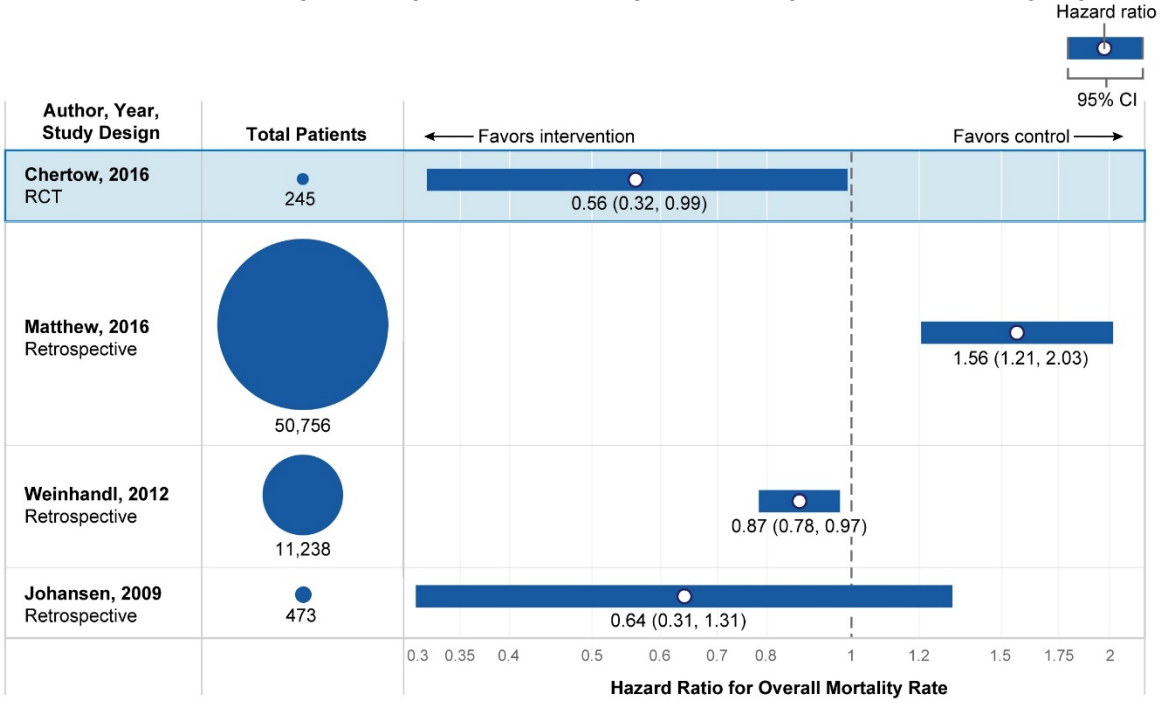
Results by Outcome

Mortality and Related Composite Endpoints

A single RCT, reported in two publications,[27, 66] and three observational studies, reported in four articles[32, 38, 44, 45] examined the effect of more frequent hemodialysis on mortality outcomes (Figure 8). During the 12-month study period, of the RCT, there were five deaths (4%) in the frequent hemodialysis arm and nine deaths (7.5%) in the control arm. Frequent hemodialysis (6 times per week) was associated with statistically significant beneficial effects on the two primary composite outcomes: of death or increase (from baseline to 12-months) in LV mass (Hazard Ratio (HR) 0.61; 95% confidence interval (CI), 0.46 to 0.82); and death or decrease (from baseline to 12-months) in physical-health composite performance (HR 0.70; 95% CI, 0.53 to 0.92), compared with thrice-weekly, incenter hemodialysis. However, since the rate of death was low in both groups, the observed treatment effect is largely attributed to the intermediate outcomes. The combined endpoint of death or hospitalization not related to hemodialysis access did not reach statistical significance (HR 0.93; 95% CI, 0.62 to 1.39). During the extended followup period to assess the long-term effects of the 12-month frequent incenter hemodialysis intervention (median followup 3.6 years), the observed mortality rate was lower in the more frequent hemodialysis group compared with the control group (4.3 versus8.2 deaths per 100 person years) resulting in a HR of 0.54 (95% CI, 0.31 to 0.93) without censoring for transplantation and HR of 0.56 (95% CI, 0.32 to 0.99) with censoring for kidney transplantation. Bayesian analyses, which were not prespecified, suggested that the actual benefit of more frequent hemodialysis might be smaller. Under a conservative prior posterior distribution of HR, the probability of an HR $\leq$0.8 was 61 percent and an HR showing harm was 7 percent. The exact probability of the observed HR was not described.[66, 68]

One retrospective cohort study[38] also showed beneficial effects of daily home hemodialysis on all-cause mortality when compared to prevalent patients from the USRDS database receiving thrice-weekly, incenter hemodialysis that were matched (1:5 ratio) on a number of patient demographics and clinical characteristics. The mortality rates were 10.0 and 12.7 per 100 person years in the frequent hemodialysis versus the usual care group over 4 years of followup (mean followup 1.8 and 1.7 years, respectively), resulting in an HR of 0.87 (95% CI, 0.78 to 0.97) (Figure 8). More frequent daily home hemodialysis was associated with a lower risk of death due to cachexia or hemodialysis withdrawal (HR 0.63; 95% CI, 0.41 to 0.95) or an unknown cause (HR 0.59; 95% CI, 0.44 to 0.79). However, the effect of more frequent daily home hemodialysis on cardiovascular disease mortality (HR 0.92; 95% CI, 0.78 to 1.09), infectious disease mortality (HR 1.13; 95% CI, 0.84 to 1.53), or other specified cause (HR 1.06; 95% CI, 0.81 to 1.37) was

Figure 8. Hazard ratios for overall mortality in studies comparing more frequent hemodialysis (greater than three times per week) with usual care (three times per week hemodialysis).*†



* The FHN trials were not designed or powered for mortality. The 3-year followup period includes 1 year of intervention phase and 2 years of observational followup during which time many participants returned to usual care.
†One randomized controlled trial: Chertow, 2016. The remainder are observational.

non-significant.[38] This study later reported on death rates with intention to treat followup of 13 and 13.5 per 100 person years (home hemodialysis and usual care group respectively).

In another study, the effect of frequent hemodialysis on risk of mortality did not significantly differ by participant characteristics, including year of daily home hemodialysis initiation, Medicare as primary payer, age, race, sex, ESRD duration, body mass index, or presence of cardiovascular disease or presence of diabetes. The patients included in this study were relatively young and healthy (mean age 53), compared with the general ESRD population. In a second retrospective cohort study[32] the mortality rates over 4 years of follow-up were 35.2 per 100 person years in the frequent hemodialysis group and 17.8 per 100 person years in the in-center, thrice weekly hemodialysis patients, matched for selected demographic and clinical characteristics (age, sex, race, central venous catheter as vascular access, and the Charlson Comorbidity Index). The more frequent incenter hemodialysis had a statistically significant higher mortality compared with in-center, thrice weekly hemodialysis patients (HR 1.56; 95% CI, 1.21 to 2.03) (Figure 8). However, patients in the more frequent group had greater weekly interdialytic weight gains, larger body mass index, and higher prevalence of fluid overload, which suggests substantial confounding by indication (see Appendix E, Evidence Table 17 through Evidence Table 19). The matching may have been inadequate to account for the confounding.[32]

A third observational study reported on composite mortality risk or major comorbid events (Figure 8).[45] Mortality rates for the usual care hemodialysis group was 139 per 1000 patient years and 91 per 1000 patient years for the shorty-daily hemodialysis group. There was a

reduced but non-significant risk of death for short daily hemodialysis compared with that for usual care hemodialysis (HR 0.64; 95%CI 0.31 to 1.31; P=0.22). The risk of death or major morbid event comparing short daily hemodialysis to usual care hemodialysis was not significant (HR 0.83, 95%CI 0.42 to 1.65; P=0.60). [45]

The findings of this one RCT and three cohort studies provided low level evidence that more frequent hemodialysis reduced the risk of death, reduced the the composite endpoints of death or increase in LV mass, and death or decrease in physical health composite score (Table 9).

Hospitalization

Four studies (one RCT and three observational) reported on the effect of more frequent hemodialysis on hospitalizations. In the 12-month followup of the FHN Daily Trial,[27] frequent hemodialysis showed no significant effect on all-cause (HR 0.88; 95% CI, 0.60 to 1.28) or cause-specific hospitalizations, including hospitalizations unrelated to vascular access (HR 0.80; 95% CI, 0.53 to 1.21), related to vascular access (HR 0.99; 95% CI, 0.54 to 1.82), cardiovascular-related (HR 0.83; 95% CI, 0.44 to 1.59), or infection-related causes (HR 0.83; 95% CI, 0.49 to 1.40).

One retrospective cohort study[33] assessed the association of frequent home hemodialysis using the NxStage System One compared with less frequent home hemodialysis using the Fresenius 2008K@home system. During the 1-year study period, no significant difference was seen in hospitalization rates between the two groups. The hospitalization rates were 1.40 and 1.59 per patient-year at risk for the frequent hemodialysis group (NxStage System One) compared with the Fresenius 2008K@home group, respectively, resulting in an IRR of 1.14 (95% CI, 0.73 to 1.78). The findings were also non-significant in the stratified analysis comparing the NxStage System One group with patients in the Fresenius 2008K@home group with a frequency of 3 to 3.49 times per week (IRR 0.88, 95% CI, 0.50 to 1.57). The observed hospitalization rates for both groups were lower than reported rates of incenter hemodialysis patients in the USRDS (see Appendix E, Evidence Table 10).

Two retrospective cohorts studies compared either registry data[44] or matched patients[45] to USRDS data. One study followed patients for 3 years and measured a composite of all cause hospitalization, non-vascular access-related hospitalization, cardiovascular hospitalization, and infection related hospitalization; hospitalization associated with congestive heart failure; and hospitalization associated with vascular accesses. No significant difference was seen for any of these hospitalization outcomes between short daily hemodialysis and usual care hemodialysis (see Appendix E, Evidence Table 10) The other study[44] reported on cumulative incidence of hospital admissions overall and cause specific, no statistics were presented. Intention to treat followup hospital admission was also reported for all cause (HR, 1.01; 95% CI, 0.98 to 1.03) as well as first admission (HR, 1.14, 95% CI, 1.09 to 1.19), and readmission (HR, 0.96, 95% CI, 0.94 to 0.99). Additionally, intention to treat specific cause admission was reported for a number of causes. Admission rates were also reported for a number of causes(Appendix e, Evidence Table 10).[45]

The findings of the one RCT, one prospective cohort, and two retrospective cohort studies provide low strength evidence on which to base a conclusion regarding the effect of more frequent hemodialysis on the risk of hospitalization, owing to the small number of studies, imprecision, and overall risk of bias (Table 10)

Table 9. Summary of the strength of evidence on mortality outcomes: more frequent hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Conclusion
Death	1 RCT (245) 3 cohorts (324,716)	RCT: Some concerns Cohorts: Serious, Critical	Direct	Inconsistent	Imprecise	Low	More frequent hemodialysis was associated with lower risk of death
Death or increase in LV mass	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a lower rate of this composite outcome
Death or decrease in PHC	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associate with a lower rate of this composite outcome
Death or hospitalization not related to hemodialysis access	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
Cardiovascular disease mortality	1 cohort (273,487)	Serious	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI

HD = hemodialysis; LV = left ventricular; NAI = not applicable due to insufficient evidence; PHC = physical health composite; RCT = randomized controlled trial

Table 10. Summary of the strength of evidence on hospitalization: more frequent hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
All-cause hospitalization	1 RCT (245) 1 cohort (138) 2 cohort (21,353)	RCT: Some concerns Cohorts: critical, serious	Direct	Consistent	Imprecise	Low
Cause-specific hospitalization	1 RCT (245) 2 cohort (21,353)	RCT: Some concerns Cohorts: critical; serious	Direct	Consistent	Imprecise	Low

RCT = randomized controlled trial

Patient-reported Quality of Life and Symptoms

One RCT, the FHN Daily Trial, in six publications, examined the effects of more frequent hemodialysis on QOL outcomes. In the 12-month followup of the FHN Daily Trial, frequent hemodialysis resulted in statistically significant improvements in patients' self-reported physical health, general health, and mental health (including the domains of emotional well-being and energy/fatigue, as measured by the RAND-36 health survey), recovery time after a hemodialysis treatment (84 minutes shorter; 95% CI, 89 minutes shorter to 80 minutes shorter), and patients' feeling thermometer score.[27, 57, 62, 65] The frequent hemodialysis group had slightly higher improvements in physical functioning (RAND-36), but the difference did not reach statistical significance.[62] No statistically significant difference was seen in physical performance using the health utilities index nor in the RAND-36 mental health domains of role limitation due to emotional problems and social functioning.[57, 62, 65] Similarly, no statistically significant differences were seen in patients' self-reported quality of sleep (as measured by the Medical Outcomes Study Sleep Problems Index (SPI II) score and hours of sleep)[64] and depressive symptoms (as measured by the Beck Depression Inventory) over 12 months.[57]

During the extended followup period to assess the long-term effects of the 12-month frequent incenter hemodialysis intervention (median followup 3.6 years) in the FHN Daily Trial, frequent hemodialysis resulted in small non-significant improvements in the Physical Composite Score of the RAND-36 health survey, suggesting that the 12-month improvements in self-reported physical health were not sustained over time (mean difference: 0.2; 95% CI, -2.6 to 3.1) (see Appendix E, Evidence Table 15 and Evidence Table 16).[66]

The RAND-36 health survey was not designed for but was validated in an ESRD population. The SPI II was neither designed specifically for, nor validated in an ESRD population.

The findings of the one RCT suggests low strength of evidence that more frequent hemodialysis leads to statistically significant improvements in several patient reported outcomes, including general health, physical health, mental health, emotional well-being, energy/fatigue, and time to recovery after completing hemodialysis. The evidence was insufficient in this one RCT to draw conclusions about other outcomes (Table 11)

Other Cardiovascular Outcomes

Two studies (1 RCT and 1 observational), in five publications, reported on the effect of more frequent hemodialysis on several other cardiovascular outcomes, including LV mass,[61] ventricular volumes,[54] systolic and diastolic blood pressure,[27, 33, 53] prescribed antihypertensive medications,[53] and heart rate variability.[67]

The findings of the one RCT and one prospective cohort study suggests low to insufficient evidence on which to base a conclusion regarding the effect of more frequent hemodialysis on

the risk of cardiovascular outcomes, owing to the small number of studies, imprecision, and risk of bias (Table 12) (see Appendix E, Evidence Table 11).

LV Mass and Ventricular Volumes

In the 12-month followup of the FHN Daily Trial, frequent hemodialysis was associated with significant reductions in LV mass, as measured by cardiac magnetic resonance imaging compared with the control group (mean difference -13.1 g; 95% CI, -21.3 to -5.0, p=0.002).[61] Reductions in LV mass were associated with reductions in systolic blood pressure. The magnitude of the reduction in LV mass was greater among patients with elevated LV mass at baseline (132 g or greater) (mean difference: - 22.7g; 95% CI, -36.7 to -8.7) compared with less than 132 g (mean difference: -3.6g; 95% CI, -12.4 to 5.2; p for interaction less than 0.0001). There was no effect modification by age, gender, diabetes, race, anthropometric volume, vintage of ESRD, or baseline urine volume. More frequent hemodialysis also had beneficial effects on ventricular volumes, including left and right ventricular end diastolic volumes and LV end systolic volume.[54] Among the 61 participants in the FHN Daily Trial with long-term followup (median 3.6 years; 10%-90% range, 1.5 to 5.3 years), the frequent hemodialysis group had sustained reductions in LV mass over time (adjusted mean change from baseline, -14.1+/- 3.4 g). This was not statistically significantly different from the control group (mean difference -8.7g; 95% CI, -17.9 to 0.5, p=0.06) (see Appendix E, Evidence Table 14).[66]

The findings of the one RCT suggests low strength of evidence that more frequent hemodialysis lowers LV mass (Table 13).

Mean Difference in Blood Pressure

In the 12-month followup of the FHN Daily Trial,[27, 53] more frequent hemodialysis lowered average pre- and postdialysis systolic blood pressure (mean difference in mmHg: -10.0; 95% CI, -13.9 to -6.0 and -7.9; 95% CI -11.8 to -3.9, respectively) and pre- and postdialysis diastolic blood pressure (mean difference in mmHg: -5.1; 95% CI, 7.4 to -2.8 and -3.4; 95%CI, -5.6 to -1.2, respectively). Frequent hemodialysis also resulted in a reduction in the number of prescribed antihypertensive medications (mean difference: -0.36, 95% CI, -0.65 to -0.08) and inter-dialytic weight gain (mean difference in kg: -1.0; 95%CI, -1.1 to -0.8).[53] One retrospective cohort study also found a beneficial effect of more frequent home hemodialysis on systolic blood pressure at the end of the 12 month study period. This study compared home hemodialysis patients receiving five or more treatments per week using NxStage System with patients receiving three or more treatments per week using Fresenius 2008K@home (133.8 mmHg; 95% CI, 129.5 to 138.1 vs. 140.3 mmHg; 95%CI, 136.0 to 144.6, respectively, p=0.04) (see Appendix E, Evidence Table 12 and Evidence Table 13).[33]

The findings of the one RCT suggests low strength of evidence that more frequent hemodialysis leads to lower systolic blood pressure, lower interdialytic weight gain, and lower antihypertensive medication use (Table 14).

Table 11. Summary of the strength of evidence on quality of life and symptom measures: more frequent hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
RAND-36 General Health Scale	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a better score on this outcome
RAND-36 Physical health composite	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a better score on this outcome
RAND-36 Physical functioning	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NA
RAND-36 Mental health composite	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a better score on this outcome
RAND-36 Emotional well-being	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a better score on this outcome
RAND-36 Energy/Fatigue	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a better score on this outcome
RAND-36 Role limitation due to emotional problems	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
RAND-36 Social functioning	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
Recovery time after hemodialysis	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with better recovery time after hemodialysis
HUI	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
SPI-II	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
BDI	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI

BDI = Beck Depression Inventory; HUI = Health Utilities Index; NAI = not applicable due to insufficient evidence; RCT = randomized controlled trial; SPI-II = Sleep Problems Index-II

Table 12. Summary of the strength of evidence on cardiovascular disease outcomes: more frequent hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
SBP	1 RCT (245) 1 cohort (138)	RCT: Some concerns Cohort: Serious	Direct	Consistent	Precise	Low	More frequent hemodialysis was associated with a reduction in SBP
DBP	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Insufficient	NAI
Number of antihypertensive medications prescribed	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a reduction in the number of antihypertensive medications
Inter-dialytic weight gain	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a reduction in inter-dialytic weight gain

DBP = diastolic blood pressure; CVD = cardiovascular disease; NAI = not applicable due to insufficient evidence; RCT = randomized controlled trial; SBP = systolic blood pressure

Table 13. Summary of the strength of evidence on LV mass: more frequent hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Reduction in LV mass as measured by MRI	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a reduction in LV mass

LV = left ventricular; RCT = randomized controlled trial

Heart Rate Variability

In the 12-month followup of the FHN Daily Trial, more frequent hemodialysis improved heart rate variability, more closely approximating normal physiology.[67] We include the detailed results in Appendix E, Evidence Table 21.

The findings of the one RCT suggests low strength of evidence that more frequent hemodialysis leads to lower heart rate variability (Table 15).

Anemia markers

Two studies (1 RCT and 1 observational), in three publications, reported on the effect of more frequent hemodialysis on the dose of erythropoietin-stimulating agents, hemoglobin, and iron-related measures.[27, 33, 55] In the 12-month followup of the FHN Daily Trial, the hemoglobin concentration increased significantly in the frequent hemodialysis group compared with usual care (mean difference: 0.33 g/dL; 95% CI, 0.05 to 0.61). The studies reported no significant effect on the dose of erythropoietin-stimulating agents (ESA) per week (mean difference in geometric means: -17.2; 95% CI, -35.8 to 6.8), total monthly intravenous iron doses (mean difference in geometric means: 86.3 mg; 95% CI, -5.88 to 268.76), ferritin levels (mean difference: -98.4 ng/mL; 95% CI, -197.6 to 0.8), or transferrin saturation (mean difference: 0.48%; 95% CI, -2.54 to 3.5).[27, 55] One retrospective cohort study found no significant differences in mean hemoglobin or the proportion of patients using erythropoietin-stimulating agents between patients receiving three or more home hemodialysis treatments per week versus patients receiving five or more treatments per week at the end of the 12-month study period (11.5 g/dl : 95% CI, 11.2 to 11.8 vs. 11.4 g/dL; 95% CI, 11.1 to 11.7, respectively, p=0.54 and 71.0%; 61.5 to 80.4 vs. 65.5; 95% CI, 55.4 to 75.5, p=0.36, respectively) (see Appendix E, Evidence Table 43).[33]

The findings of the one RCT, and one observational study suggest low strength of evidence that more frequent hemodialysis leads to improvement in hemoglobin levels. The evidence was insufficient to draw conclusions for other outcomes (Table 16).

Metabolic/Nutritional Measures

Two studies (1 RCT and 1 observational), in five publications, reported on the effect of more frequent hemodialysis on metabolic and nutrition related measures.[27, 50-52, 60] The full results can be found in Appendix E, Evidence Table 9. In the 12-month followup of the FHN Daily Trial, frequent hemodialysis was associated with a reduction in pre-hemodialysis serum phosphorous and phosphorous binder dose compared with the usual care (mean difference in grams per day: -0.46; 95% CI, -0.78 to -0.13 and -1.35; 95% CI, -2.50 to -0.20, respectively).[27, 60] The treatment effect on change in serum phosphorous was more pronounced among participants with higher serum phosphorus at baseline with relative reduction in serum phosphorous at 12 months of 0.32 (SD 0.12 mg/dl) for every 1 mg/dl higher baseline serum phosphorous (p for interaction=0.009). There was no significant difference between groups in serum parathyroid hormone level (26.0% difference in geometric means; 95% CI, -3.4% to 64%), serum calcium (data not reported), or dialysate calcium (treatment effect not reported). Frequent hemodialysis was also associated with an increase in bicarbonate levels (mean difference in mmol per liter: 0.86, 95%CI, 0.02 to 1.70).[50] There was no significant change in thyroid function measures, including thyroid stimulating

Table 14. Summary of the strength of evidence on mean difference in blood pressure: more frequent hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
SBP	1 RCT (245) 1 cohort (138)	RCT: Some concerns Cohort: Serious	Direct	Consistent	Precise	Low	More frequent hemodialysis was associated with lower SBP
DBP	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Insufficient	NAI
Number of antihypertensive medications prescribed	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with reduction in antihypertensive medication use.
Inter-dialytic weight gain	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with less interdialytic weight gain

NAI = not applicable due to insufficient evidence; RCT = randomized controlled trial

Table 15. Summary of the strength of evidence, heart rate variability: more frequent hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Heart rate variability improvement	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a decrease in heart rate variability

RCT = randomized controlled trial

Table 16. Summary of the strength of evidence on anemia markers: more frequent hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Hemoglobin concentration	1 RCT (245) 1 cohort (138)	RCT: Some concerns Cohort: Serious	Direct	Inconsistent	Imprecise	Low	More frequent hemodialysis was associated with improvement in this outcome
ESA dose	1 RCT (245)	RCT: Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
ESA use	1 cohort (138)	Cohort: Serious	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI

ESA = erythropoiesis-stimulating agent; NAI = not applicable due to insufficient evidence; RCT = randomized controlled trial

hormone (mean difference in uIU/mL: -0.35; 95% CI, -0.76 to 0.07), free thyroxine (mean difference in ng/dL: 0.03: 95% CI, -0.05 to 0.12), and tri-iodothyronine (mean difference in pg/mL: 0.14; 95% CI, 0.10 to 0.38), comparing frequent hemodialysis to usual care.[51]

In the 12-month followup of the FHN Daily Trial, frequent hemodialysis did not result in sustained improvements of albumin (mean difference in g/dL: 0.03; 95% CI, -0.04 to 0.10) or a difference in equilibrated protein catabolic rate (relative difference in grams per day: 0.82; 95% CI, -2.54 to 4.19).[27, 59] Additional weight and body composition measures can be found in detail in Appendix E, Evidence Table 44.

One retrospective cohort study found no significant differences in serum calcium, phosphorus, parathyroid hormone, albumin, or normalized protein catabolic rate at the end of the 12-month study period comparing home hemodialysis patients receiving five or more treatments per week using NxStage System versus patients receiving three or more treatments per week using Fresenius 2008K@home.[33] (see Appendix E, Evidence Table 6, Evidence Table 7, Evidence Table 9)

The findings of the one RCT, and one observational study suggest low strength of evidence that more frequent hemodialysis leads to lower serum phosphorus, lower phosphorus binder dose, and higher bicarbonate levels. The evidence was insufficient to draw conclusions for other outcomes (Table 17).

Adverse Events/Harms

One RCT assessed potential harms associated with more frequent hemodialysis.[27] In the 12-month followup of the FHN Daily Trial, the percentage of treatments associated with intradialytic hypotension requiring lowering of ultrafiltration rate, reduced blood flow, or administration of saline was lower in the frequent hemodialysis group compared with the control group (10.9% vs. 13.6%, p=0.056).[27, 53] However, owing to the greater number of treatments in the frequent hemodialysis group, frequent hemodialysis was associated with a higher absolute number and greater risk of hemodialysis treatments with intradialytic hypotension (HR 1.53; 95% CI, 1.11 to 2.09) (see Appendix, Evidence Table 13).[53] Frequent hemodialysis was also associated with greater risk of receiving interventions related to vascular access with control. In the frequent hemodialysis group, 47 (37.6%) of the patients required at least one intervention compared to 29 (24.2%) of the patients in the control group. For the frequent hemodialysis group compared to the control group, the HR for the time to first vascular intervention was 1.71 (95% CI, 1.08 to 2.73), however, for the recurrent event analysis, the HR was 1.35 (95% CI, 0.84 to 2.18). Interventions to correct access failure occurred in 15 (12%) of the patients in the frequent hemodialysis group (19 events) and 15 (12.5%) of the patients in the control group (23 events). No difference was seen in rates of hypokalemia less than 3.5 mmol per liter (4.2% vs. 6.4%, p=0.57) or hypophosphatemia of less than 2.17 mg per deciliter (5.8% vs. 7.2%, p=0.80) (see Appendix E, Evidence Table 48).[27] Frequent hemodialysis was not associated with faster decline in residual kidney function.

The findings of the one RCT suggests low strength of evidence that more frequent hemodialysis leads to lower proportion of hemodialysis treatments with intradialytic hypotension and higher risk of vascular access complications. The evidence was insufficient regarding other harms (Table 18).

Table 17. Summary of the strength of evidence on metabolic/nutritional markers: more frequent hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Metabolic/ nutritional measures							
Serum phosphorous	1 RCT (245) 1 cohort (138)	RCT: Some concerns Cohort: Serious	Direct	Inconsistent	Precise	Low	More frequent hemodialysis was associated with improvement in this outcome
Phosphorous binder dose	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with improvement in this outcome
Serum PTH	1 RCT (245) 1 cohort (138)	RCT: Some concerns Cohort: Serious	Direct	Consistent	Imprecise	Insufficient	NA
Bicarbonate levels	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Low	More frequent hemodialysis was associated with improvement in this outcome
Serum Calcium	1 cohort (138)	Serious	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
Thyroid function measures (TSH, fT4, T3)	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
Albumin	1 RCT (245) 1 cohort (138)	RCT: Some concerns Cohort: Serious	Direct	Consistent	Imprecise	Insufficient	NAI
Normalized protein catabolic rate	1 RCT (245) 1 cohort (138)	RCT: Some concerns Cohort: Serious	Direct	Consistent	Imprecise	Insufficient	NAI

fT4 = free thyroxin; NAI = not applicable due to insufficient evidence; PTH = parathyroid hormone; RCT = randomized controlled trial; T3 = triiodothyronine; TSH = thyroid stimulating hormone

Table 18. Summary of the strength of evidence on adverse events/harms: more frequent hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Vascular access complications	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with an increase in vascular access complications
Intradialytic hypotension	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent hemodialysis was associated with a reduction in intradialytic hypotension
Hypokalemia	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
Hypophosphatemia	1 RCT (245)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI

NAI = not applicable due to insufficient evidence; RCT = randomized controlled trial

Key Question 3

Does extended hemodialysis duration (daytime, 4 or more hours per treatment, or nocturnal, overnight) improve objective outcomes over the long term (more than six months) compared with usual length hemodialysis duration (less than 4 hours)?

Key findings

- One RCT and five observational studies reported the effects of longer hemodialysis on outcomes.
- Patients included in all the RCTs and most of the observational studies were comparable to the overall U.S. hemodialysis population regarding age and racial demographics.
- The evidence was insufficient to determine whether longer hemodialysis, compared with usual care, had clinically important effects on mortality, QOL, blood pressure, or metabolic parameters.

The impact of more frequent hemodialysis was presented above for KQ 2. To address whether longer duration of hemodialysis improved outcomes compared with usual duration, the below section reports studies examining longer hemodialysis duration as the intervention.

Description of Included Studies

Six studies compared the effect of longer hemodialysis duration compared with usual care, including five observational studies and one RCT (Table 19). These studies were published between 2007 and 2019 (Table 19).

The five observational studies[36, 40-43] analyzed a total number of patients between 16 to 88,153. From these studies, between 16 and 26,917 patients were analyzed who had received a hemodialysis treatment that was longer than 4 hours. The one RCT was the Time to Reduce Mortality in End-Stage Renal Disease (TiME) Trial, which screened 10,287 patients and ultimately assigned 7,035 patients to usual care (3,966 patients) or hemodialysis treatment durations of 4.25 hours or more (3,069 patients).[29] Followup ranged from 10 months to 5 years (Table 20).

Interventions varied across studies, including analyzing cohorts of patients with various durations of hemodialysis to randomizing patients to the intervention. The prospective study by Troidle invited 16 patients to participate in the thrice weekly nocturnal program at 8 hours per treatment, with comparison with their pre-nocturnal experience.[42] The other observational studies compared nocturnal or extended hours patients with patients receiving a usual care duration of hemodialysis,[36, 40],or used analytic methods to compare those receiving 4 or more hours of hemodialysis with those receiving less than 4 hours of hemodialysis at large hemodialysis organizations.[41, 43] The TiME Trial randomized 266 facilities to assign their patients to usual care or hemodialysis treatments lasting 4.25 hours or more, and then assigned patients at these facilities to their intervention strategy.[29]

Study populations were heterogenous. The mean age of participants was 51.5 to 66.7 years. Sex distribution was also heterogenous with percentages of female participants between 12 percent and 61 percent. Studies also reported heterogeneous race and ethnicity, with a mean of

Table 19. Summary of characteristics of randomized trials of the duration of hemodialysis.

Author, year	Study name Study design	N patients (n in treatment arm) Recruitment period	Number of study centers Dialysis location	Comparison
Dember, 2019[29]	TIME RCT	7035 (3069) 2013 to 2015	DaVita; Fresenius Home and In-center	Frequency: three treatments per week Duration: 3.5 hours per treatment Frequency: three treatments per week Duration: ≥4.25 hours per treatment

LDO = large dialysis organization; RCT = randomized controlled trial; TiME = Time to Reduce Mortality in End-Stage Renal Disease Trial;

Table 20. Summary of characteristics of observational trials of the duration of hemodialysis.

Author, year	Study name Study design	N patients (n in treatment arm) Recruitment period	Number of study centers Dialysis location	Comparison
Brunelli, 2010[43]	ArMORR cohort Prospective	8552 (3773) 2004 to 2005	Fresenius Dialysis center	Frequency: three treatments per week Duration: 3.02 to 3.98 hours per treatment Frequency: three treatments per week Duration: ≤3 hours per treatment Frequency: three treatments per week Duration: ≥4 hours per treatment
Lacson, 2012[36]	NR Prospective	2808 (959) 2006 to 2007	Fresenius Home and Dialysis center	Frequency: three treatments per week Duration: 3.75 Hours per treatment Frequency: three treatments per week Goal duration: >5.5 hours per treatment
Miller, 2010[41]	NR Retrospective	88,153 (26,917) 2001 to 2006	DaVita Dialysis center	Frequency: three treatments per week Duration: <3 hours per treatment Frequency: three treatments per week Duration: 3 to <3.5 hours per treatment Frequency: three treatments per week

Author, year	Study name Study design	N patients (n in treatment arm) Recruitment period	Number of study centers Dialysis location	Comparison
				Duration: 3.5 to <4 hours per treatment Frequency: three treatments per week Duration: ≥4 hours per treatment
Rivara, 2016[40]	NR Observational: retrospective	112,913 (1206) 2007 to 2011	DaVita Dialysis center	Frequency: three treatments per week Duration: 211 minutes/treatment Frequency: three treatments per week Duration: 399 minutes/treatment
Troidle, 2007[42]	NR Prospective	16 (16) 2005 to NR	Multicenter Dialysis center	Pre-nocturnal Frequency: NR Goal duration: NR Nocturnal Frequency: three treatments per week Goal duration: 8 hours per treatment

ArMORR = Accelerated Mortality on Renal Replacement cohort; LDO = multiple dialysis clinics managed by a large dialysis organization; NR = not reported; USRDS = United States Renal Data System;

37 percent to 59.5 percent White/Caucasian, 23.7 percent to 63 percent Black/African-American, 0 percent to 14.5 percent Latino/Hispanic, and the remainder other races and ethnicities. The TiME Trial further accounted for the impact of body habitus by stratifying their analyses based on whether patients had an estimated body water less than or equal to 42.5 L, which represented 64 percent of their patients (see Appendix E, Evidence Table 1 through Evidence Table 4).[29]

Owing to the heterogeneous nature of the study design, populations, and particular way the outcomes were measured, we were not able to conduct a meta-analysis. We are synthesizing the individual study results below, including direction and magnitude of associations.

Results by Outcome

Mortality and Related Composite Endpoints

Five studies reported the association of extended hemodialysis treatments on overall mortality rate (Figure 9)**.** The TiME Trial did not show a statistically significant difference between groups in overall mortality.[29] The TiME Trial was terminated early (median followup, 1.1 years) owing to an inadequate between group difference in treatment duration (goal, 45 minutes; achieved, 9 minutes). In their full analysis population, the rate of death was 16.8 per 100 person years in the extended hemodialysis group and 17.4 per 100 person years in the usual care group, corresponding to an HR of 0.97 (95% CI, 0.85 to 1.12). This mortality rate is similar to that reported for U.S. incident hemodialysis patients (16.6 per 100 person years). The subgroup of patients with lower estimated body water had similar associations.

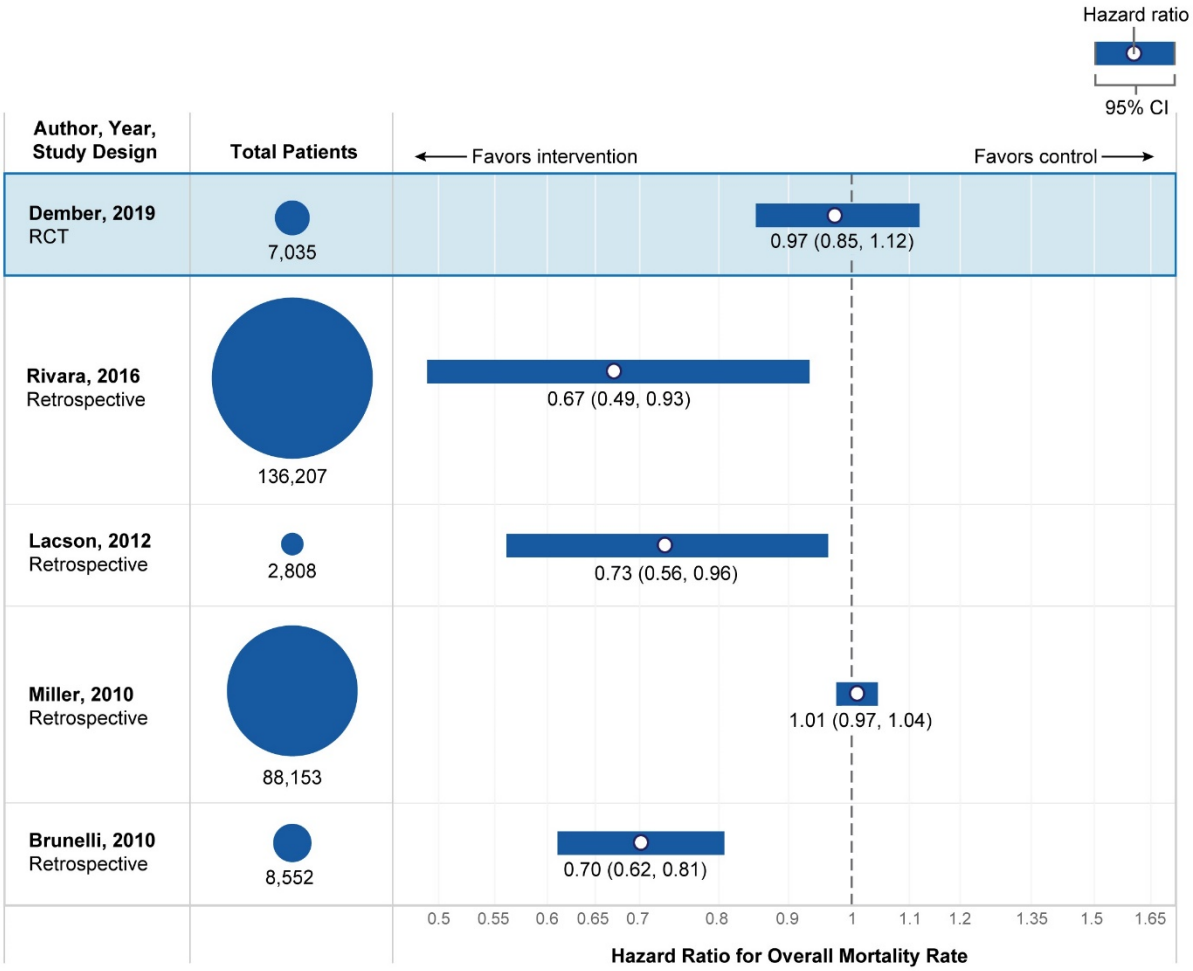
Unlike the TiME Trial, the observational studies did show a significantly lower risk of death in those receiving longer hemodialysis treatments. For the nocturnal and extended-hours studies,

the crude mortality rate in those receiving extended treatments were lower than the TiME Trial at 6.4 per 100 person years in the Rivara study[40] and 9 percent at one year in the Lacson study.[36] The crude mortality rates in the usual care group in these studies were 14.7 per 100 person years and 15 percent, respectively. This gave an adjusted HR of 0.67 (95% CI, 0.49 to 0.93) overall in the Rivara study, and an adjusted HR of 0.73 (95% CI, 0.56 to 0.96) at 1 year in the Lacson study, both statistically significant. Additional modeling assumptions and longer duration of outcome assessment showed similar relationships in these studies.

In studies analyzing total time of hemodialysis in large hemodialysis organizations, the results also showed a statistically significant association between extended hemodialysis and lower mortality, but these associations were attenuated and no longer significant after adjustment for differences in confounding factors. In the study by Miller and colleagues which used time-dependent Cox-proportional hazards regression models, the authors reported that longer hemodialysis treatment was associated with greater survival. However, in multivariate-adjusted models including Kt/V, no obvious difference was observed between a duration of 3.5 to less than 4 hours and a duration of 4 hours or more. The exact relationships were not provided other than in figure form.[41] The study by Brunelli and colleagues used multivariable adjusted analysis and marginal structural models to compare the association between mortality and hemodialysis duration of less than 4 hours or greater than or equal to 4 hours. The study population overlapped with the Miller study. Shorter duration of hemodialysis (less than 4 hours) compared with longer duration (4 or more hours) was associated with a higher risk of death in the marginal structural model (HR 0.70; 95% CI, 0.62 to 0.81), but not in the time-updated multivariable adjusted models (HR 1.00, 95% CI, 0.88 to 1.15) (see Appendix E, Evidence Table 33 and Evidence Table 34).[43]

The findings of one RCT and four observational studies suggest insufficient evidence that longer hemodialysis impacts the risk of death, owing to the small number of studies, and inadequate separation of randomized groups (in the TiME trial), and high-to-serious risk of bias (Table 21).

Figure 9. Hazard ratios for overall mortality in studies comparing longer duration hemodialysis (4 or more hours per treatment) compared with usual care hemodialysis (less than 4 hours per treatment).*



*One randomized controlled trial: Dember, 2019. The remainder are observational.

Table 21. Summary of the strength of evidence on mortality: longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
Death	1 RCT (7,035) 4 observational (2,808; 8,552; 88,153; 112,913)	RCT: High risk of bias Cohorts: Moderate, Serious	Direct	Consistent	Precise	Insufficient

RCT = randomized controlled trial

Patient Reported Quality of Life and Symptoms

Two studies reported the difference in QOL comparing extended hemodialysis with usual care. At baseline and 6 months, one study examined 16 patients who started the nocturnal program and used the mental and physical component scales from the SF-36, the Beck Depression Inventory (BDI), the Fatigue Scale, and time to recovery.[42] This study reported no significant changes in these scores at 6 months, though it did report a trend toward improved depression and time to recovery at 6 months. The TiME Trial used the Kidney Disease Quality of Life Short From-36 (KDQOL-36) collected within 4 months of hemodialysis initiation and annually thereafter, as part of routine clinical care.[29] It further separated out the physical component score, mental component score, effect of kidney disease scale, burden of kidney disease scale, and symptoms and problems scale.

The mean (standard deviation (SD)) in each scale ranged from 37.4 (10.8) to 81.0 (14.0) across time points. When comparing the intervention and usual care groups, no statistically significant differences were seen in the change in each component's scores, with p-values ranging from 0.07 to 0.63 (see Appendix E, Evidence Table 32).

The KDQOL-36 health survey was both designed for and validated in an ESRD population. Both the SF-36 and the BDI were not designed specifically for and ESRD population but were validated in an ESRD population.

The findings of one RCT and one observational study suggest insufficient evidence that longer hemodialysis impacts QOL, owing to the small number of studies, imprecise estimates, and high-to-serious risk of bias (Table 22).

Hospitalization

Only the TiME Trial reported differences in hospitalization rates comparing extended duration hemodialysis with usual care.[29] It reported that hospitalization rates were 195.4 and 203.4 per 100 person years in the intervention and usual care group in the full analysis population (p=0.39). Results were similar in the analysis of those patients with lower estimated body water (p=0.44) (see Appendix E, Evidence Table 28 and Evidence Table 29).

The findings of one RCT provides insufficient evidence that longer hemodialysis impacts the risk of hospitalization, owing to a single study with high risk of bias (Table 23).

Table 22. Summary of the strength of evidence on quality of life and symptom measures: longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
KDQOLSF-36	1 RCT (7,035)	High risk of bias	Direct	Single Study (not applicable)	Imprecise	Insufficient
SF-36	1 pre-post (16)	Serious	Direct	Single Study (not applicable)	Imprecise	Insufficient
BDI	1 pre-post (16)	Serious	Direct	Single Study (not applicable)	Imprecise	Insufficient
The Fatigue Scale	1 pre-post (16)	Serious	Direct	Single Study (not applicable)	Imprecise	Insufficient
Time to recovery	1 pre-post (16)	Serious	Direct	Single Study (not applicable)	Imprecise	Insufficient

BDI = Beck Depression Inventory; KDQOL SF-36 = Kidney Disease Quality of Life, Short Form 36; RCT = randomized controlled trial; SF-36 = Short Form 36

Table 23. Summary of the strength of evidence on hospitalization: longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
Hospitalization rate	1 RCT (7,035)	High risk of bias	Direct	Single Study (not applicable)	Imprecise	Insufficient

RCT = randomized controlled trial

Blood Pressure and Related Parameters

Blood pressure measurements were not standardized in any of the studies. Changes in systolic blood pressure were reported in the TiME Trial,[29] the study by Lacson,[36] and the study by Troidle.[42]. The TiME Trial reported both predialysis systolic blood pressure and predialysis diastolic blood pressure.[29] No significant differences were seen in these parameters at the end of the study. In the full analysis cohort, mean (SD) predialysis systolic blood pressure in the intervention group was 143.0 (19.0) and 143.4 (19.1) mmHg in the control group (p=0.26). In the full analysis cohort, mean (SD) predialysis diastolic blood pressure in the intervention group was 74.8 (11.5) and 74.6 (11.3) mmHg in the control group (p=0.63). Similar findings were seen in the subgroup with lower estimated total body water.

In the Lacson study,[36] patients in the incenter nocturnal group started with a lower predialysis systolic blood pressure than the usual care group, though this was not statistically significant (p=0.1). The authors reported patients in both the usual care hemodialysis group and the incenter nocturnal hemodialysis group had a statistically significant decrease in blood pressure by the end of 180 days (p<0.0001 and p=0.0003, respectively, versus baseline). When comparing the absolute difference in blood pressure between groups at the end of 180 days, the blood pressure in the incenter nocturnal group was lower (p=0.03). In the Troidle study of 16 patients,[42] the mean (SD) postdialysis systolic blood pressure was 136 (14) mm Hg in the baseline period, and 128 (14) mm Hg in the nocturnal period; number and type of blood pressure agents used were not described.

Both Lacson[36] and Troidle[42] demonstrated a lower ultrafiltration rate in the group receiving nocturnal hemodialysis, whereas the TiME Trial[69] showed no significant difference between groups. The TiME Trial[69] and Lacson study[36] also reported interdialytic weight gain between treatments. In the TiME Trial's full analysis population, those incident patients receiving hemodialysis in facilities randomized to prescribe longer hemodialysis gained an average (SD) of 1.93 (0.98) kg, while those receiving usual care hemodialysis gained an average (SD) of 1.88 (1.00) kg; these results were not significantly different (p=0.28). On the other hand, Lacson reported significantly higher weight gain in those receiving nocturnal hemodialysis, with p<0.0001 compared with baseline at both 3 and 6 months, and p<0.0001 compared with usual care hemodialysis at both 3 and 6 months (see Appendix E, Evidence Table 30 and Evidence Table 31).

The findings of one RCT and two observational studies suggests insufficient evidence that longer hemodialysis impacts blood pressure related parameters, owing to the small number of studies, inconsistent associations, imprecise estimates, and high to serious risk of bias (Table 24).

Table 24. Summary of the strength of evidence on blood pressure and related parameters: longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
SBP	1 RCT (7,035), 2 observational (16; 2,808)	RCT: High risk of bias Cohorts: Serious	Direct	Inconsistent	Imprecise	Insufficient
DBP	1 RCT (7,035)	High risk of bias	Direct	Single Study (not applicable)	Imprecise	Insufficient

DBP = diastolic blood pressure; RCT = randomized controlled trial; SBP = systolic blood pressure

Anemia Markers

The Lacson study[36] was the only study to report differences in hemoglobin comparing incenter usual care hemodialysis with incenter nocturnal hemodialysis. At the end of 180 days, the group receiving nocturnal hemodialysis had a statistically significant increase in hemoglobin compared with their baseline ($p<0.0001$. They also began at a slightly lower baseline hemoglobin ($p=0.04$) compared with the control group's baseline. This yielded a change in hemoglobin in the nocturnal group that was larger than the usual care group (0.4 g/dl vs. 0.1 g/dl). The final hemoglobin in the nocturnal group was not significantly different from the usual care group ($p=0.06$) (see Appendix E, Evidence Table 23).

The findings of one observational study suggests insufficient evidence that longer hemodialysis impacts anemia markers, owing to a single study, imprecise estimates, and serious risk of bias (Table 25).

Metabolic/Nutritional Measures

Two studies reported outcomes of metabolic and nutritional markers comparing longer hemodialysis with usual care hemodialysis. For changes in serum phosphorus, the two studies examining this question both showed a lower serum phosphorus in those receiving nocturnal hemodialysis.[36, 42] The Troidle study found the mean phosphorus level in patients on usual care hemodialysis was 5.3 mg/dL compared with 4.4 mg/dL after being on nocturnal hemodialysis; this was statistically significant ($p=0.049$). The Lacson study reported a sustained, statistically significant decline in phosphorus levels from 5.73 to 5.02 mg/dl ($p<0.001$) was observed with conversion to incenter nocturnal hemodialysis, whereas matched period prevalent (usual care hemodialysis) patients' phosphorus levels increased minimally during followup from 5.75 to 5.85 mg/dl ($p=0.01$). The phosphorus comparison between nocturnal and usual care groups at the end of 3 and 6 months were also statistically significantly lower in the nocturnal group ($p<0.0001$ at both times).

The Troidle[42] and Lacson[36] studies also reported serum calcium changes between groups, though findings were not consistent across studies. The Troidle study found the mean (SD) calcium level of patients while on usual care hemodialysis was 9.3 (1.0) mg/dL and after being on nocturnal hemodialysis was 9.3 (0.81) mg/dL; this was not statistically significant ($p=0.94$). The Lacson study reported a small (0.1 to 0.2 mg/dl) sustained, significant ($p<0.001$) increase of mean serum calcium was observed in the incenter nocturnal hemodialysis group, with minimal change in usual care hemodialysis controls. The calcium comparison between groups at the end of 3 and 6 months also showed it was significantly higher in the nocturnal group ($p=0.0008$ and $p=0.0002$, respectively).

Table 25. Summary of the strength of evidence on anemia markers: longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
Hemoglobin concentration	1 cohort (2,808)	Serious	Direct	Single Study (not applicable)	Imprecise	Insufficient

Finally, Lacson[36] reported a change in serum albumin comparing usual care hemodialysis with nocturnal hemodialysis. They reported that patients receiving nocturnal hemodialysis began with a lower albumin but had higher levels at followup. The increase in albumin at 6 months in the nocturnal group was 0.6 g/dl ($p<0.0001$ versus baseline), compared with 0.2 g/dl ($p=0.003$ versus baseline) in the usual care group. No differences existed between usual care and nocturnal groups at any of the time points (see Appendix E, Evidence Table 24).

The findings of two observational studies suggests insufficient evidence that longer hemodialysis impacts metabolic and nutritional parameters, owing to the limited number of studies and the serious risk of bias (Table 26).

Adverse events

The TiME Trial[29] was the only one to report postdialysis hypotensive episodes, defined as postdialysis systolic blood pressure less than 90 mm Hg. In the full analysis population, 539 (17.6%) patients in the intervention group had hypotensive events, and 774 (19.5%) patients in the usual care group had hypotensive events. This yielded 75.2 (95% CI, 51.2 to 110.4) events per 100 person years in the intervention group, 68.1 (95% CI, 51.8 to 89.6) events per 100 person years in the usual care group, and a rate ratio of 1.11 (95% CI, 0.69 to 1.77). Similar findings were seen in the subgroup with lower estimated total body water.

Other harms were not explicitly listed but could be indirectly reflected through adherence to therapy. No significant differences were seen in adherence to hemodialysis treatments in the TiME Trial, where 83.3 percent of patients in the usual care and 82.3 percent in the intervention group experienced a missed hemodialysis treatment. However, treatment duration did decrease over time, impacting the intervention group more than the control group. The authors indicated that both facility and patient factors were responsible for not achieving the desired 4.25 hours per treatment in the intervention group. Facility factors included perceptions by nephrologists and staff of lack of need for longer hemodialysis or potential burden. Patient factors included unwillingness to have longer hemodialysis treatments.

Table 26. Summary of the strength of evidence on metabolic/nutritional markers: longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
Phosphorus level changes	2 observational (16; 2,808)	Serious	Direct	Consistent	Imprecise	Insufficient
Calcium level changes	2 observational (16; 2,808)	Serious	Direct	Inconsistent	Imprecise	Insufficient
Albumin level changes	1 cohort (2,808)	Serious	Direct	Single Study (NA)	Precise	Insufficient

NA= not applicable

The nocturnal study by Troidle reported patient concerns of longer, nocturnal hemodialysis as "I don't like sitting in these chairs for 8 hours," and "I have trouble sleeping."[42] The Lacson study reported that 42 percent of active patients were still receiving intermittent nocturnal hemodialysis at 2 years[36]. Finally, the Brunelli study using administrative data[43] reported that 82.2 percent of patients continued to have hemodialysis duration of 4 or more hours at 3 months, and an additional 82.2 percent of those continued to have hemodialysis duration of 4 or more hours at 6 months. Risk factors for not continuing longer duration hemodialysis were not reported.

The TiME Trial[29] reported the frequency of hypokalemia (serum potassium less than 3.6 mEg/L), hypophosphatemia (serum phosphorus less than 3.0 mg/dl), hyperbicarbonatremia (serum bicarbonate greater than 26 mmol/L), and hypoalbuminemia (serum albumin less than 3.2 g/dl) across both groups. In the full analysis population, the usual care group had a higher risk of hypokalemia but lower risk of hypophosphatemia, hyperbicarbonatremia, and hypoalbuminemia than the intervention group; none of these reached statistical significance (p=0.07, 0.06, 0.13, 0.79, for each respective outcome comparison).

The Lacson study also reported changes in white blood cell count[36], which could be a marker of inflammation or infection. They reported a statistically significant decreased white blood cell count at 3 months (p=0.0002) and 6 months (p=0.0006) in those receiving nocturnal hemodialysis. This was not significantly different from the values in the conventional group (p=0.2 at both 3 months and 6 months) (see Appendix E, Evidence Table 35 through Evidence Table 39).

None of the studies reported any data on access thrombosis or complications.

The findings of one RCT and two observational studies suggest insufficient evidence that longer hemodialysis impacts adverse events, owing to a limited number of studies, imprecise estimates, and high to serious risk of bias (Table 27).

Table 27. Summary of the strength of evidence on adverse events/harms: longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
Hypotensive events	1 RCT (7,035)	High risk of bias	Direct	Single Study (not applicable)	Imprecise	Insufficient
Hypokalemia	1 RCT (7,035)	High risk of bias	Direct	Single Study (not applicable)	Imprecise	Insufficient
Hypophosphatemia	1 RCT (7,035)	High risk of bias	Direct	Single Study (not applicable)	Imprecise	Insufficient
Hyperbicarbonatremia	1 RCT (7,035)	High risk of bias	Direct	Single Study (not applicable)	Imprecise	Insufficient
Hypoalbuminemia	1 RCT (7,035)	High risk of bias	Direct	Single Study (not applicable)	Imprecise	Insufficient
Adherence to therapy	1 RCT (7,035) 3 observational (16; 2,808; 8,552)	RCT: High risk of bias Observational: Serious	Direct	Inconsistent	Imprecise	Insufficient
Changes in white blood cell count	1 cohort (2,808)	Serious	Direct	Single Study (not applicable)	Imprecise	Insufficient

RCT = randomized controlled trial

Key Questions 2 and 3 Combined:

Does more frequent and extended hemodialysis duration (greater than three times per week and daytime, 4 or more hours per treatment, or nocturnal, overnight) improve objective outcomes over the long term (more than six months) compared with usual hemodialysis frequency and duration (three times per week and less than 4 hours)?

Key Findings

- One RCT, one non-randomized controlled trial, and five observational studies reported the effects of more frequent and longer hemodialysis on outcomes.
- Patients included in the RCT and most of the observational studies were slightly younger than, and just as likely to be white compared with the overall U.S. hemodialysis population.
- The strength of evidence was low that more frequent and longer hemodialysis, compared with usual care, may be associated with:
  - Improvements in several blood pressure related parameters, including lower predialysis systolic and diastolic blood pressure, lower interdialytic weight gain, lower ultrafiltration rate, less intradialytic hypotension, and lower antihypertensive medication use;
  - Shorter time to recovery after completing hemodialysis treatment; and
  - Lower levels of predialysis serum phosphorus and higher levels of predialysis serum bicarbonate.
  - More vascular access events;
  - Loss of residual kidney function.
- The evidence was insufficient to determine whether more frequent and longer hemodialysis, compared with usual care, had any effects on mortality, LV mass, or patient reported outcomes.

Description of Included Studies

Seven studies, including five observational studies, one non-randomized controlled trial (reported in two studies), and one RCT (18 publications),[28, 31, 45, 50-57, 59-65, 70] compared the effect of both more frequent and longer hemodialysis with usual care. These studies were published between 1997 and 2019. The five observational studies[34, 35, 37, 39, 45] analyzed a total number of patients that ranged from 49 to 1,726. In these five studies, the number of patients that received both more frequent and longer hemodialysis ranged from 18 to 338. One of these studies, by Dixon,[39] had 21 patients (11 in the intervention arm) out of 49 that overlapped with the FHN Nocturnal trial. The study by Hladunewich,[34] described outcomes for 22 pregnant women in Canada treated with more frequent and longer hemodialysis compared with 70 pregnant women in the U.S. who had shorter treatment time. The study followup time ranged from 9 months to 12 years. The one non-randomized controlled trial (reported in two articles) screened 108 patients and then assigned 26 consecutive patients that agreed to participate to the intervention arm.[30, 31] The only RCT was the FHN Nocturnal trial, which enrolled 118 patients and, ultimately,

randomized 87 patients at nine sites in the U.S. and Canada: 42 to usual care and 45 to nocturnal hemodialysis.[28] The number of patients screened was not reported. The planned enrollment for the FHN Nocturnal trial was 250 patients, which was subsequently reduced to 90 patients due to recruitment challenges.[28] Followup time for the FHN Nocturnal trial was 12 months for the initial RCT period followed by an extended followup period, which included 52 of 87 randomized patients, for a median of 3.7 years.[70]

The observational studies analyzed different methods and locations for administering frequent and longer hemodialysis. The study by Lockridge reported use of nocturnal home hemodialysis using the Fresenius 2008K machine.[37] The study by Dixon also reported use of nocturnal home hemodialysis.[39] Eighteen patients were on nocturnal hemodialysis, of which 11 were included in the FHN trial. No other details were provided for the hemodialysis regimen of the remaining seven participants. The method for administering more frequent or longer hemodialysis was not reported in the studies by Hladunewich,[34] or Nesrallah[35] (the article specified it was not administered using the NxStage device). Johansen[45] compared patients receiving nocturnal hemodialysis to a usual care hemodialysis population in the USRDS database. The non-randomized controlled trial used short, daily incenter hemodialysis at a rate of 6 treatments per week and 3 hours per treatment.[30, 31] The hemodialysis machine used was not reported. The FHN Nocturnal trial randomized patients at 10 sites to either three treatments per week (usual care) or six treatments at night (intervention group). All patients were dialyzed at home; the hemodialysis machine used to deliver these treatments was not described.[28]

Study populations were heterogenous (Table 28 and Table 29). Non-US participants were included in the observational studies by Hladunewich[34] and Nesrallah[35], and the FHN Nocturnal trial.[28] The mean age of participants ranged from 27 to 54 years. Sex distribution was also heterogenous with women constituting 32 percent to 100 percent of the study populations. Studies reported a diversity of race and ethnicity, with a mean of 0 percent to 68 percent White/Caucasian, 4 percent to 51 percent Black/African American, 0 percent to 92 percent Latino/Hispanic, and the remainder of other races and ethnicities (see Appendix E, Evidence Table 1 through Evidence Table 4).

Owing to the heterogeneous nature of the study design and populations, and the way the outcomes were measured, we were not able to conduct a meta-analysis. We are synthesizing the individual study results below, including direction and magnitude of associations.

Results by Outcome

Mortality and Related Composite Endpoints

Four studies reported the association of frequent and longer hemodialysis with mortality (Figure 10). For the FHN Nocturnal trial, the results for the two primary endpoints were not statistically significant. For the endpoint of death or change in LV mass, the resulting HR was 0.68 (95% CI, 0.44 to 1.07) and, for the endpoint of death or change in physical health composite score, the HR was 0.91 (95% CI, 0.58 to 1.43).[28] The FHN Nocturnal trial was not powered to assess mortality as a primary endpoint. Three deaths occurred during 12 months of the RCT followup period[28] and 19 deaths during the extended post trial observational followup (5 patients died in the thrice weekly home hemodialysis arm and 14 patients died in the frequent nocturnal home hemodialysis arm). The overall observed mortality rate in the post RCT observational phase (3 per 100 person years) was very low compared with the overall mortality rate for the U.S. hemodialysis population (16.6 per 100 person years). However, the HR for all cause

Table 28. Summary of characteristics of randomized and non-randomized trials of the frequency and duration of hemodialysis.

Author, year	Key question	Study name Study design	N patients (n in treatment arm) Recruitment period	Number of study center Dialysis location	Comparison
Ayus, 2005[30] Achinger, 2013[31]	2	NR CCT	77 (26) 2003 to 2004	(Dialysis West, Texas Diabetes Institute) Home and In-center	Frequency: three treatments per week Duration: 4 hours per treatment Frequency: six treatments per week Duration: 3 hours per treatment
Rocco, 2011*[28, 50-67, 70]	2-3	FHN-Nocturnal RCT	87 (45) 2006 to 2009	(multiple LDOs and single sites) Home	Frequency: six treatments per week Duration: 1.5 to 2.75 hours per treatment Frequency: three treatments per week Duration: ≥6 hours per treatment

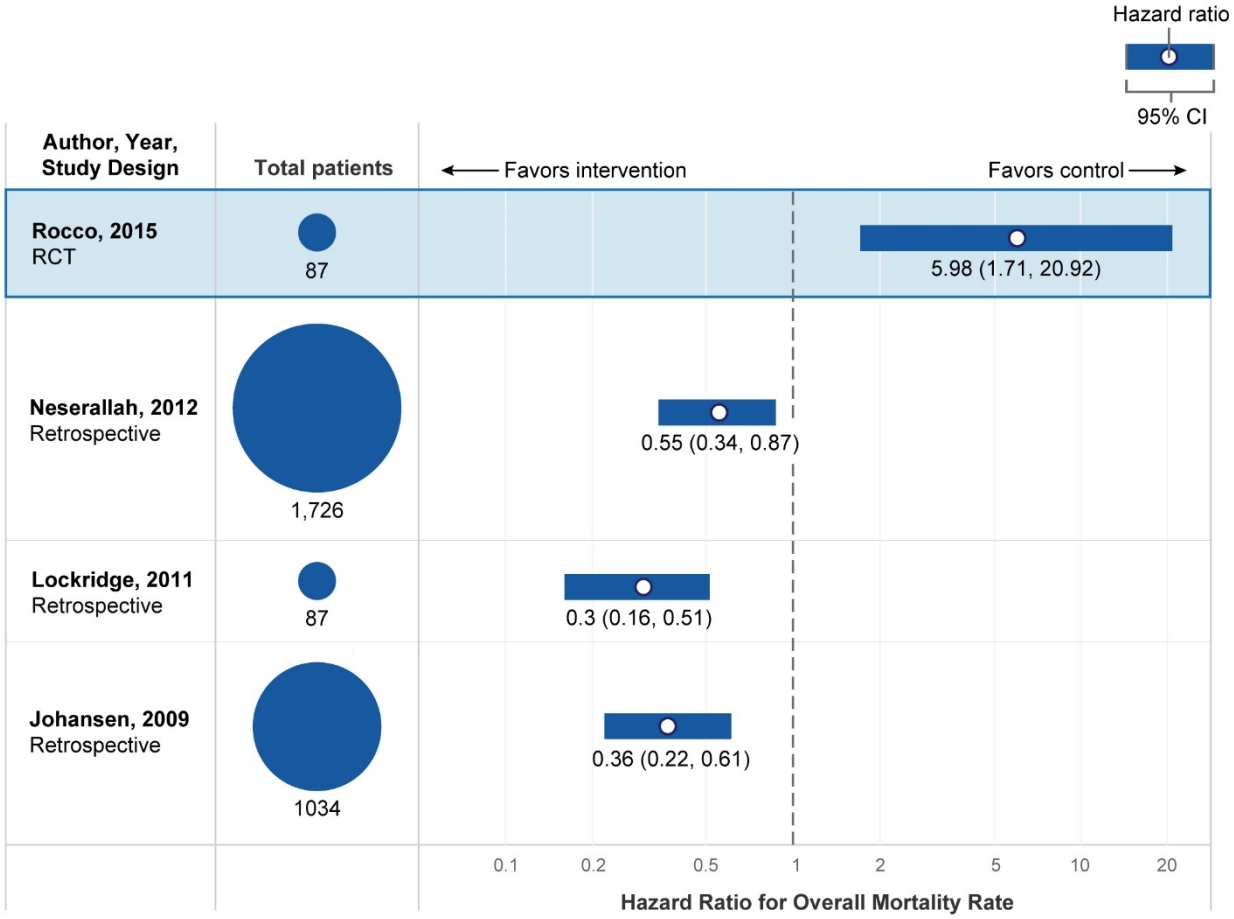
FHN = Frequent Hemodialysis Network; LDO = large hemodialysis organization; RCT = randomized controlled trial; NR = not reported; CCT = controlled clinical trial
*This is the main study article. Subsequent articles are cited.

Table 29. Summary of study characteristics of observational studies of the frequency and duration of hemodialysis.

Author, year	Key question	Study name Study design	N patients (n in treatment arm) Recruitment period	Number of study center Dialysis location	Comparison
Dixon, 2016[39]	2-3	NR Prospecti ve	77 NR	Multicenter Home and Dialysis center	Frequency: three treatments per week Duration: ≥7.5 hours per week Frequency: six treatments per week Duration: 36 hours per week Frequency: Not applicable Duration: NR
Hladunewich, 2014[34]	2-3	Toronto PreKid Retro-spective	Toronto PreKid: 22 pregnancies US ARPD Cohort: 70 pregnancies 2000 to 2013	Multicenter Home	Duration: 0 to 20 hours per week Duration: 21 to 36 hours per week Duration: 37 to 56 hours per week
Johansen, 2009[45]	2-3	NR Retro-spective	1034 (94) 1997-2006	Home (intervention) In-center (usual care)	Frequency: 3 treatments per week Duration: 3.5 hours per treatment Frequency: 5-6 sessions (days) per week Duration: 7.5 hours per treatment
Lockridge, 2011[37]	2-3	NR Retro-spective	USRDS: NR NHHD: 87 1997 to 2009	Multicenter Home and Dialysis center	Frequency: three treatments per week Duration: 40 hours per week, 7 hours per treatment
Nesrallah, 2012[35]	2-3	NR Retro-spective	1726 (338) 2000 to 2010	Multicenter Home and Dialysis center	Frequency: three treatments per week Goal duration: <5.5 hours per treatment Frequency: three to seven treatments per week Goal duration: >5.5 hours per treatment

ARPD = American Registry for Pregnancy in Dialysis Patients; LDO = large hemodialysis organization; NR = not reported; USRDS = United States Renal Data System; NHHD = nocturnal home hemodialysis

Figure 10. Hazard ratios for overall mortality in studies comparing more frequent and longer duration hemodialysis (greater than three times per week and 4 or more hours per treatment) compared with usual care hemodialysis (three times per week and less than 4 hours per treatment).*†



*SMR data

* The FHN trials were not designed or powered for mortality. The 3-year followup period includes 1 year of intervention phase and 2 years of observational followup during which time many participants returned to usual care.
†One randomized controlled trial: Rocco, 2015. The remainder are observational.

mortality comparing frequent nocturnal home hemodialysis to thrice weekly home hemodialysis was 3.88 (95% CI, 1.27 to 11.79) without censoring at transplantation, and 5.98 (95% CI, 1.71 to 20.92) with censoring for transplantation.[70] During this observational phase, there was a high rate of switching of hemodialysis frequency and duration. In an as treated analysis, using a 6-month running average of intervention as exposure, nocturnal home nocturnal hemodialysis was not associated with higher risk of mortality (HR 1.19; 95% CI, 0.44 to 3.21). Bayesian analyses, which were not prespecified, suggested that the observed harm with HR of 5.98 in the intention to treat analysis, was highly implausible. Under a conservative prior posterior distribution of HR, the probability of harm was 88 percent and of a small benefit with an HR between 0.8 and 1 was 11 percent. The exact probability of the observed HR was not described.[68, 70]

In contrast to the results of the FHN Nocturnal trial, the observational studies reported survival benefits for more frequent and longer hemodialysis. In the study by Nesrallah,[35] the mortality rate was 6.1 per 100 person years in the frequent and longer hemodialysis group and 10.5 per 100 person years in the matched, in-center, thrice weekly hemodialysis patients, resulting in an HR of 0.55 (95% CI, 0.34 to 0.87). In the study by Lockridge, the mortality rate for frequent nocturnal home hemodialysis group was 8.4 per 100 person years. The standardized mortality ratio, comparing the study population with the mortality rate reported by the United

States Renal Data System, was 0.30 (95% CI, 0.16 to 0.51). The study by Johansen[45] reported a mortality rate of 74 per 1000 patient years in the nocturnal hemodialysis group compared to 154 per 1000 patient years in the usual care hemodialysis group with a HR of 0.36 (95% CI, 0.22 to 0.61) (Figure 10) (see Appendix E, Evidence Table 65 through Evidence Table 69).[37]

The findings of one RCT and three prospective cohort studies insufficient evidence that more frequent and longer hemodialysis impact the risk of mortality, because of the small number of studies, imprecision, inconsistency, and moderate to critical risk of bias in the observational studies (Table 30).

Table 30. Summary of the strength of evidence on mortality and related composite endpoints: more frequent and longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
Deaths	1 RCT (87) 3 cohorts (2847)	RCT: some concerns Cohorts: critical (2), moderate	Direct	Inconsistent	Imprecise	Insufficient
Infection-related mortality	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
CVD mortality	1 RCT (87) 1 cohort (1034)	RCT: Some concerns Cohort: critical	Direct	Consistent	Imprecise	Low
Death/LV mass composite	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
Death/PHC composite	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
Non-access related hospitalization or death	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient

CVD = cardiovascular disease; RCT = randomized controlled trial.

Patient Reported Quality of Life and Symptoms

One study, the FHN Nocturnal trial, included patient reported outcomes in a total of four publications.[57, 62, 64, 65] During the 12-month followup of this study, more frequent and longer nocturnal home hemodialysis compared with thrice weekly home hemodialysis was associated with 63 minutes faster time to recovery after hemodialysis (95% CI, 54 to 71 minutes).[62] However, the trial found no between group improvements in other QOL measures, including physical health composite and physical functioning subscales of the RAND-36,[65] Sleep Problem Index (SPI),[64] Beck Depression Inventory (BDI),[57] and time to recovery (see Appendix E, Evidence Table 63 and Evidence Table 64).[62]

The RAND-36, and BDI were not designed specifically for and ESRD population but were validated in an ESRD population. The SPI was neither designed for not validated in an ESRD population.

The findings of one RCT suggests insufficient evidence that more frequent and longer hemodialysis impacts patient reported QOL and symptoms, except for time to recovery, for which the strength of evidence was judged as low (Table 31).

Left Ventricular Mass

Two studies measured LV mass and reported on change with more frequent and longer hemodialysis. The FHN Nocturnal trial measured LV mass by magnetic resonance imaging and found no difference in LV mass between the two arms of the trial after 12 months of followup (mean change, -10.9 grams; 95% CI, -23.7 to 1.8).[61] Those patients with LV mass less than 132 g at baseline had a greater reduction in LV mass compared with those with LV mass greater than or equal to 132 g. The authors did not test for statistical significance owing to small sample sizes. No differences were seen in LV mass in a number of other subgroups, including those defined by age, sex, race, and presence of diabetes mellitus.[61] In the study by Ayus,[30] LV mass, calculated by echocardiographic parameters, decreased at 12 months after a switch from thrice weekly in center hemodialysis to short daily hemodialysis (mean change, -46 grams; 95% CI [estimated from figure] 62.3 to -29.7; $p<0.0001$) (Figure 11) (see Appendix E, Evidence Table 61).

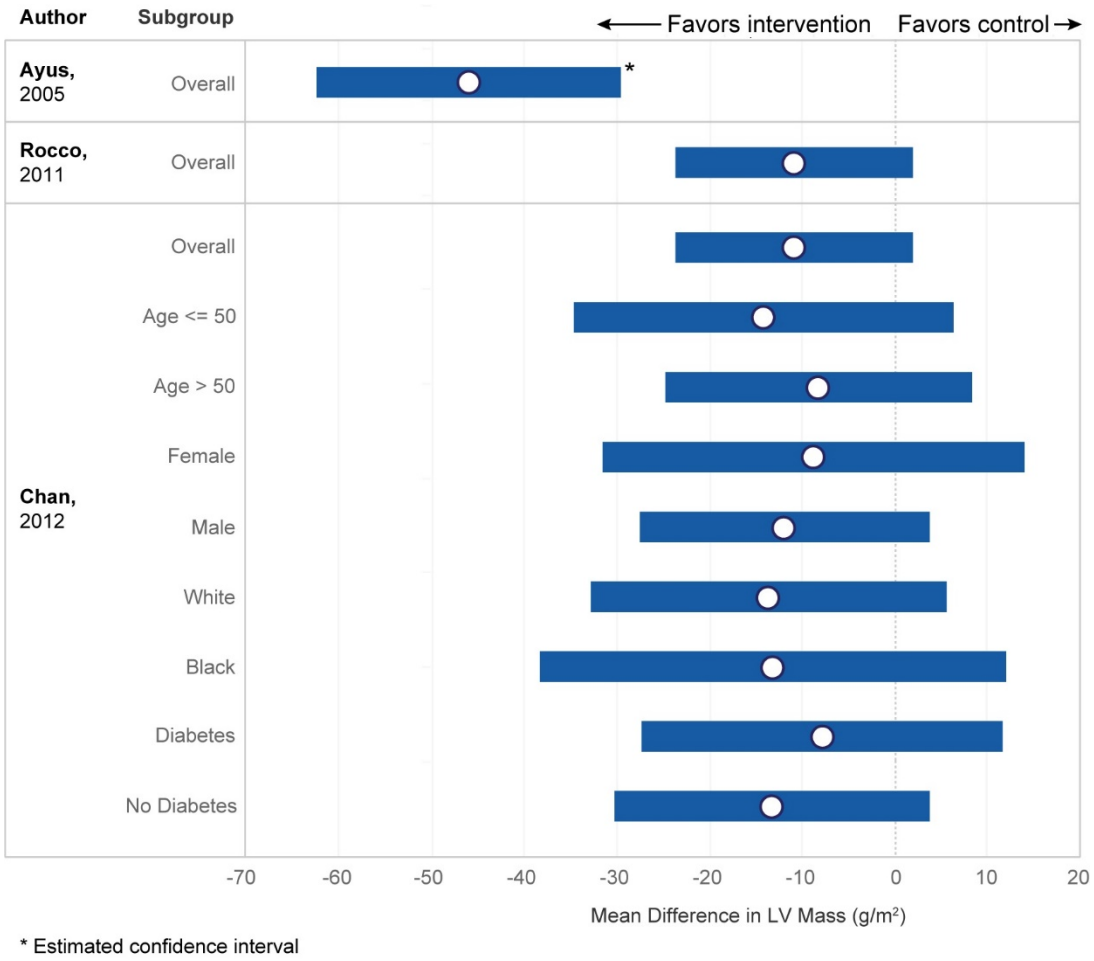
The findings of one RCT and one observational study suggest insufficient evidence that more frequent and longer hemodialysis impacts LV mass. (Table 32).

Table 31. Summary of the strength of evidence on patient reported QOL and symptoms: more frequent and longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
Time to recovery	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Precise	Low
SPI-II score	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
RAND-36 PHC	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
RAND-36 Emotional Well-being	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
RAND-36 Energy/Fatigue	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
RAND-36 Mental Health Composite	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
RAND-36 Physical Functioning	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
RAND-36 Role limitation due to emotional problems	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
RAND-36 Social Functioning	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
HUI-3 Score	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
General health scale	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
BDI	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient
BDI-Cognitive Subscale	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient

BDI = Beck Depression Inventory; CVD = cardiovascular disease; HUI = health utilities index; PHC = decrease in physical-health composite performance; QOL = quality of life; RCT = randomized controlled trial; SPI-II = sleep problems index II; SPPB = Short Physical Performance Battery

Figure 11. Mean differences in LV mass in RCTs comparing more frequent and longer duration hemodialysis (greater than three times per week and 4 or more hours per treatment) compared with usual care hemodialysis (three times per week and less than 4 hours per treatment).



LV = left ventricular; RCT = randomized controlled trial
* 95% CI estimated from figure.

Table 32. Summary of the strength of evidence on LV mass: more frequent and longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
Left ventricular mass	1 RCT (87), 1 cohort (77)	RCT: Some concerns Cohort: Moderate	Direct	Inconsistent	Imprecise	Insufficient

LV = left ventricular; RCT = randomized controlled trial

Blood pressure and related parameters

Blood pressure measurements were not standardized in any of the studies. Changes in blood pressure were reported in the FHN Nocturnal trial[53] and the non-randomized controlled trial by Ayus[30]. In the FHN Nocturnal trial, the between group comparison of change in predialysis systolic blood pressure from baseline to 12 months showed that the systolic blood pressure was lower in the group receiving more frequent and longer hemodialysis (mean difference -8.0 mm Hg; 95% CI, -1.6 to -14.5 mm Hg). The changes in blood pressure were observed starting at 2 months after randomization.[53] Postdialysis blood pressure did not show a statistically significant difference between the groups. At 12 months, the nocturnal group had lower interdialytic weight gain (-0.46 kg; 95% CI, -0.77 to -0.15), lower ultrafiltration rates (-4.1 ml/min; 95% CI, -5.4 to -2.8), and fewer prescribed antihypertensives (-0.44; 95% CI, -0.89 to -0.09). However, no between group differences were seen in total body water, intracellular water, or extracellular water body composition measured using bioelectrical impedance.[59] In the study by Ayus, there was no significant decrease in blood pressure in the intervention group at 12 months (see Appendix E, Evidence Table 60).[30]

The findings of one RCT and one non-randomized trial, suggests low strength of evidence that more frequent and longer hemodialysis is associated with lower predialysis systolic and diastolic blood pressure, lower interdialytic weight gain, lower ultrafiltration rate, and less antihypertensive medication use (Table 33).

Anemia Markers

In the FHN Nocturnal trial, no differences were seen in any of the anemia related parameters except monthly intravenous iron dose, which was lower in the nocturnal arm (mean monthly dose difference, -66.6 mg; 95% CI, -88.5 to -2.51).[55] In the non-randomized controlled trial by Ayus, the hemoglobin was higher ($p<0.0001$) and the erythropoietin dose was lower ($p<0.01$) in the more frequent and longer hemodialysis arm compared with usual care.[30] Between group difference in these parameters was not reported (see Appendix E, Evidence Table 77).

The findings of one RCT and one observational study suggests insufficient evidence that more frequent and longer hemodialysis impacts anemia markers (Table 34).

Metabolic/Nutritional Measures

Several studies reported outcomes of metabolic and nutritional markers comparing frequent and longer hemodialysis with usual care hemodialysis. In the FHN Nocturnal trial, phosphorus levels were lower (mean between group difference, -1.4 mg/dL; 95% CI, -2.1 to -0.7) in the intervention group compared with usual care, but serum albumin was unchanged.[28, 59] Serum bicarbonate levels, reported in only a subset of participants (n=18), were higher in the intervention group (mean between group difference, 2.99 mEq/L; 95% CI, 1.41 to 4.56).[50] There were no significant between group differences in body weight or bioelectrical impedance derived measures for lean body mass and adiposity.[59] In the non-randomized controlled trial by Ayus, serum albumin and serum calcium increased in the intervention group but was unchanged in the usual care group.[30] Serum phosphorus, serum C-reactive protein, and oral calcium acetate use also decreased in the intervention group; however, between group differences were not reported (see Appendix E, Evidence Table 41 through Evidence Table 51).

Table 33. Summary of the strength of evidence on blood pressure and related parameters: more frequent and longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Predialysis change in blood pressure	1 RCT (87), 1 cohort (77)	RCT: Some concerns Cohort: Moderate	Direct	Inconsistent	Precise	Low*	More frequent or longer duration of hemodialysis improves this outcome.
Postdialysis change in blood pressure	1 RCT (87), 1 cohort (77)	RCT: Some concerns Cohort: Moderate	Direct	Inconsistent	Imprecise	Insufficient	NAI
Antihypertensive medication use	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Precise	Low*	More frequent or longer duration of hemodialysis improves this outcome.
Interdialytic weight gain	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Precise	Low*	More frequent or longer duration of hemodialysis improves this outcome.
Ultrafiltration rate	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Precise	Low*	More frequent or longer duration of hemodialysis improves this outcome.

NAI = not applicable due to insufficient evidence; RCT = randomized controlled trial

* The strength of evidence was graded as low rather than insufficient because the results were precise enough to rule out a clinically important benefit. The results were not precise enough to determine if hemodialysis produced an increase or no difference in the risk of CIN.

Table 34. Summary of the strength of evidence on anemia markers: more frequent and longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
Hemoglobin	1 RCT (87), 1 cohort (77)	RCT: Some concerns Cohort: Moderate	Direct	Inconsistent	Imprecise	Insufficient
Erythropoietin supplementation agent use	1 cohort (77)	Cohort: Moderate	Direct	Single Study (not applicable)	Imprecise	Insufficient

RCT = randomized controlled trial

The findings one RCT and one non-controlled trial suggest low strength of evidence that more frequent and longer hemodialysis is associated impacts lowering of serum phosphorus and an increase in serum bicarbonate. The evidence is insufficient to draw conclusions regarding the effect of more frequent and longer hemodialysis on other metabolic and nutritional parameters (Table 35).

Adverse Events/Harms

In the FHN Nocturnal trial, the risk of intradialytic hypotension was lower in the nocturnal group (relative risk 0.35; 95% CI, 0.18 to 0.69) compared with usual care.[30] There was a trend toward higher vascular access complications in the intervention arm. In the nocturnal group, 51 percent of patients suffered a vascular access failure or underwent at least one vascular access procedure compared with 36 percent of patients in the control arm (HR, 1.88; 95% CI, 0.97 to 3.64).[30] Loss of residual kidney function was also more pronounced in the nocturnal arm. All of the 87 participants in the FHN Nocturnal trial had residual kidney function (non-zero urine output) at baseline.[56] By 12 months, 36 percent of the participants in the thrice weekly arm and 67 percent of the participants in the nocturnal arm were anuric (p=0.06).[56] No differences were seen in hypokalemia or hypophosphatemia between the two groups.[56]

Vascular access outcomes were also reported in one non-randomized trial.[31] Seventy-seven patients were followed for up to 48 months. These patients received either usual care hemodialysis or daily hemodialysis or daily hemodialysis (Table 28). There was no significant difference between groups in frequency of total vascular access procedures; rates of fistulagram, thrombectomy, or access revision; time to first access procedure (Appendix E, Evidence Table 73).

In the observational study by Lockridge,[37] a number of other complications were reported in the nocturnal group, including endotoxin shock from contaminated water, needle dislodgement, and catheter disconnection (see Appendix E, Evidence Table 40, Evidence Table 70 through Evidence Table 76).[37]

The findings of one RCT and one observational study suggests low strength of evidence that more frequent and longer hemodialysis impacts lower risk of intradialytic hypotension, higher risk of access complications, and faster decline in residual kidney function. The evidence is insufficient to draw conclusions regarding the effect of more frequent and longer hemodialysis on other adverse events (Table 36).

Pregnancy

Pregnancy outcomes were reported in one observational study which compared pregnancy outcomes from 22 pregnancies in the Toronto registry (from 2000 to 2013) to 70 pregnancies in the U.S. registry (from 1990 to 2011). The study reported a higher live birth rate (86.4% versus 61.4%; p=0.03) and longer duration of pregnancy (36 weeks vs. 27 weeks; p=0.002), in the Canadian cohort versus the American Cohort, respectively (see Appendix E, Evidence Table 74).[34]

The findings of one observational study suggests insufficient evidence that more frequent and longer hemodialysis impacts pregnancy outcomes (Table 37).

Table 35. Summary of the strength of evidence on metabolic/nutritional measures: more frequent and longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Serum phosphorus	1 RCT (87), 1 cohort (77)	RCT: Some concerns Cohort: Moderate	Direct	Consistent	Precise	Low	More frequent and longer duration of hemodialysis was associated with lower serum phosphorus
Serum albumin	1 RCT (87), 1 cohort (77)	RCT: Some concerns Cohort: Moderate	Direct	Inconsistent	Imprecise	Insufficient	NAI
Serum bicarbonate	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Precise	Low	More frequent and longer duration of hemodialysis was associated with higher serum bicarbonate.
Serum calcium	1 cohort (77)	Cohort: Moderate	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
Serum C-reactive protein	1 cohort (77)	Cohort: Moderate	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
Oral calcium acetate	1 cohort (77)	Cohort: Moderate	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
Body composition	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI

NAI = not applicable due to insufficient evidence; RCT = randomized controlled trial

Table 36. Summary of the strength of evidence on adverse events/harms: more frequent and longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Vascular access complications	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Low	More frequent and longer duration of hemodialysis was associated with more vascular access complications.
Loss of residual kidney function	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Low	More frequent and longer duration of hemodialysis was associated with greater loss of residual kidney function
Endotoxin shock, needle dislodgment, catheter disconnection	1 cohort (87)	Critical	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
Intradialytic hypotension	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Precise	Low*	More frequent and longer duration of hemodialysis was associated with a reduction in intradialytic hypotension.
Hypokalemia	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI
Hypophosphatemia	1 RCT (87)	Some concerns	Direct	Single Study (not applicable)	Imprecise	Insufficient	NAI

NAI = not applicable due to insufficient evidence; RCT = randomized controlled trial

Table 37. Summary of the strength of evidence on pregnancy outcomes: more frequent and longer duration hemodialysis compared with usual care hemodialysis.

Outcome	Studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence
Live birth rate	1 cohort (22 pregnancies)	Serious	Direct	Single Study (not applicable)	Imprecise	Insufficient

Key Question 4

What instruments have been used to measure QOL and symptoms in studies of people with ESRD treated by dialysis?

Key Findings

- One hundred sixty-five studies reported on in 185 articles using 125 different QOL and symptom measurement tools. Ten tools were specifically designed to measure QOL or symptoms in patients with ESRD treated by dialysis. Six tools were designed for a non-ESRD population but validated in populations with ESRD treated by dialysis.
- Data on reliability and validity was available for the most commonly used ESRD specific and ESRD validated tools.
- Minimal clinically important difference was rarely reported in studies evaluating QOL and symptom tools.
- Placebo effect was not specifically reported on in the included studies, but we were able to estimate the placebo effect in two double blind placebo-controlled trials. The placebo effect was detected in one trial using the Kidney Disease Quality (KDQ) instrument and in another trial using multiple subscales of the SF-36.
- The quality of the QOL and symptom measure tools, as measured using COSMIN, was variable. Using the median of the items within each COSMIN domain:
  - The Dialysis Symptom Index (DSI) was assessed as "good" in five of six quality domains assessed
  - The KDQOL-36 was assessed as "good" in the four of five quality domains evaluated.
  - The Pediatric Quality of Life instrument (PedsQL) was assessed as "good" in five of the seven quality domains evaluated and poor in one domain.
  - The remaining tools received variable assessments across domains.

We conducted an in-depth examination of the instruments that have been used to measure QOL and symptoms in studies of people with ESRD treated by dialysis. This part of the report is intended to enhance understanding of the QOL and symptom measures data presented in the sections on KQs 2 and 3. It also offers broader insights that will be relevant to future studies of interventions for improving QOL and symptom measures for people with ESRD treated by dialysis.

Description of Included Studies

Randomized Controlled Trials

Twenty-three RCTs, reported in 38 articles, addressed KQ 4. Three large trials were reported on in 18 articles: the FHN trial in 12 articles,[27, 28, 51, 57, 62-66, 70-72] the Hemodialysis (HEMO) Study in five articles,[73-77] and the TiME trial in one article.[29] The remaining 20 RCTs were reported on in 20 articles. The FHN trial addressed both KQ 2 and KQ 3, and the TiME trial addressed KQ 3. The three large trials (FHN, HEMO, and TiME) followed their participants for

at least 1 year. The remaining RCTs followed their participants for 2 weeks to 20 months (see Appendix F, Evidence Table F1; Table 38).

Twenty of the 23 RCTs included patients receiving treatment in a dialysis center. The other 3 took place in home or other settings. The FHN trial included multiple study sites (in-center, home, or home or in-center) (see Appendix F, Evidence Table F1; Table 38). Most studies included only adult patients. The FHN study cohort in the daily trial included patients aged 13 years and older. One additional RCT included a child population (i.e., patients aged 3 to 21 years). The language requirement for most studies was English, or English or Spanish. Race and ethnicity were either not explicitly reported or heterogeneous across studies (see Appendix F, Evidence Table F2; Table 38).

The FHN study included two trials: the daily trial compared usual care hemodialysis frequency with more frequent hemodialysis; the nocturnal trial compared usual care hemodialysis with more frequent and longer hemodialysis. The HEMO study compared low dose and high dose hemodialysis urea clearance and low flux and high flux hemodialysis membranes. The TiME trial compared usual care hemodialysis duration with longer hemodialysis duration. Of the remaining RCTs, three compared usual care hemodialysis with more frequent or longer hemodialysis.

Cohort Studies

One hundred forty-two cohort studies were relevant to KQ 4 and were reported in 147 articles. Two studies were reported in seven articles: the Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements Study (FREEDOM) reported in three articles,[78-80] and the HEMO Cohort Study reported in four articles.[81-84] The four HEMO Cohort Study articles used the above HEMO study population but was not randomized. (see Appendix F, Evidence Tables F1 and F2, and Table 38). One of the cohort studies also addressed KQ 3,[42] but none of these cohort studies addressed KQ 2. Participants in the cohort studies were followed for 1 month to 3 years.

Cohort studies primarily took place incenter (91 of 144). Over half of the cohort studies did not state a requirement for population age. Sixty-two of the remaining studies included adults only. Similar to the RCTs, the language requirement for most studies was English, or English or Spanish. Race and ethnicity were either not explicitly reported or heterogeneous across studies (see Appendix F, Evidence Table F2 Table 38).

For details on the remainder of the RCTs and cohort studies, see Appendix F, Evidence Tables F3 and F4, and Table 39.

Participant Characteristics

The RCTs included between six and 7,035 individuals. The range is broader in the cohort studies: from nine to 71,012 individuals. For KQ 4 we did not specify a minimum followup period for inclusion of studies. The percentage of females across the studies ranged from 25 to 83.3 percent in cohort studies and from 38 to 70.9 percent in RCTs. Mean age ranged from 49.1 to 74.4 years in the RCTs, and 47.2 to 67 years in the cohort studies (adult populations only). The mean age of participants in pediatric studies was 12.1 years. Race, education, and smoking status were heterogeneous across populations (see Appendix F, Evidence Table F5; Table 40).

Table 38. Characteristics of studies reporting on a quality of life or symptom tool used in dialysis patients.

Study Design: study name, n studies*	Study years	Intervention location, number of articles	Comparison	Age inclusion criteria in years	Language	Race/ ethnicity	Incident/ Prevalent
RCT: FHN, 12	2006-2009	In-center, 7 home or incenter center; 5	Conventional vs. more frequent (daily); or more frequent and longer duration (nocturnal)	>13 (daily) >18 (nocturnal)	English or Spanish	Not listed	Prevalent
RCT: HEMO, 5	1995-2000	In-center, 5	Low dose, high dose; low flux; high flux HD	18 or older	Not listed	Not listed	Prevalent
RCT: TiME, 1	2012-2015	In-center, 1	Conventional vs. longer duration	18 or older	Not listed	Not listed	Prevalent
All other RCTs: 20	1984-2018 NR: published between 2000-2017	Remainder: In-center: 17 Other: 2 NR: 1	3 usual care vs. more frequent or longer dialysis See Appendix F, Evidence table F3 for details on other interventions	Adult (>18), 16 Child (3-21), 1 Not listed, 7	English, 7 English or Spanish, 1 Not listed, 15	White non-Hispanic, 1Not listed, 18	Prevalent, 6 Not reported, 14
Cohort: FREEDOM, 3 Prospective, 2 Cross sectional, 1	2002 to 2009	Home, 2 In-center, 1	Shorter duration hemodialysis	Adults: >18 years old	English	Generally not reported. One study looked at an African-American subpopulation	Prevalent
Cohort: HEMO Cohort, 4 Prospective, 1 Cross sectional, 2	1995 to 2000	In-center, 3	Low dose, high dose; low flux; high flux HD	Adults: 18 to 80	English	Not reported	Prevalent
All other cohort studies, 140 Prospective, 70 Retrospective, 16 Interview, 1 Cross sectional, 27 Quasi-exp. 1 Pre post, 4 Survey, 5 Other or NR, 18	1970 – 2016 NR: published between 1982 - 2019	In-center, 87 Home, 1 Home or In-center, 18 Other or NR, 31	Varies across studies: See Appendix F, Evidence Table F4 for details	Adults (>18), 58 studies (in 59 articles) Child (<18), 4 NR, 70	English, 25 English or Spanish, 10 English or French, 1 NR, 103	Black non-Hispanic, 5 Mexican-American, 1 White or black non-Hispanic, 2 NR, 131	Prevalent, 21 Incident, 11 NR, 107

FHN = Frequent Hemodialysis Trial; FREEDOM = Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements; HD = hemodialysis; HEMO = the Hemodialysis (HEMO) Study; HTN = hypertension; NR = not reported; Quasi-exp = quasiexperimental; TiME = Time to Reduce Mortality in End-Stage Renal Disease Trial
* RCTs: 21 studies in 36 articles; Cohort studies: 139 studies in 144 articles

Table 39. Other outcomes reported in studies using a quality of life or symptom tool in dialysis patients.

Study Design: study name, n studies*	Metabolic	HTN control	Morbidity	Mortality	Harms	other
RCT: FHN, 12	Y	Y	Y	Y	Y	N
RCT: HEMO, 5	Y	Y	Y	Y	N	N
RCT: TiME, 1	N	Y	Y	Y	N	Y
All other RCTs: 20	Y, 6	Y, 3	Y, 2	N	Y,	Y, 7
Cohort: FREEDOM, 3 Prospective, 2 Cross sectional, 1	N	N	N	N	N	Y, 1
Cohort: HEMO Cohort, 4 Prospective, 1 Cross sectional, 2	N	N	N	N	N	N
All other cohort studies, 140 Prospective, 70 Retrospective, 16 Interview, 1 Cross sectional, 27 Quasi-exp. 1 Prepost, 4 Survey, 5 Other or NR, 18	Y, 6	Y, 1	Y, 10	Y, 10	Y, 1	Y, 8

FHN = Frequent Hemodialysis Trial; FREEDOM = Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements; HEMO = the Hemodialysis (HEMO) Study; HTN = hypertension; RCT = randomized controlled trial; TiME = Time to Reduce Mortality in End-Stage Renal Disease Trial

Table 40. Participant characteristics in studies reporting on a quality of life or symptom tool used in dialysis patients.

Study Design: study name, n studies*	Number of study participants	Followup period	% female range	Age in years	Race/ethnicity, range of mean %*
RCT: FHN, 12	Daily, 245 Nocturnal, 87	1 to 3.7 years (range of means)	38 to 62	49.1 to 65 (range of means)	White: 34 to 60 Black: 26 to 50 Latino/Hispanic: 69
RCT: HEMO, 5	1864	2.84+/-1.84 years (mean)	55 to 56.2	56.4 to 63.3 (range of means)	White: 34 to 36 Black: 43.7 to 65 Latino/Hispanic: 13.1 to 14.5
RCT: TiME, 1	7035	1.1 years (median)	58.8	66.6 (mean)	White: 55.7 to 56.4 Black: 23.7 to 24.7 Latino/Hispanic: NR
All other RCTs: 20	Range: 6-1846	2 weeks to 20 months	38 to 70.9	42.7 to 74.4	White: 15 to 55 Black: 7 to 65.4 Latino/Hispanic: 6 to 51
All cohort, 142 studies in 147 articles	9 to 71012	48 studies: 1 month to 3 years	25 to 83.3	Child: 12.1 (mean, 1 study) Adult; 47.2 to 74.4 (mean, 133 studies)	2 studies 100 White 8 studies 100 Black†

FHN = Frequent Hemodialysis Trial; FREEDOM = Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements Study; HEMO = the Hemodialysis (HEMO) Study; RCT = randomized controlled trial; TiME = Time to Reduce Mortality in End-Stage Renal Disease Trial

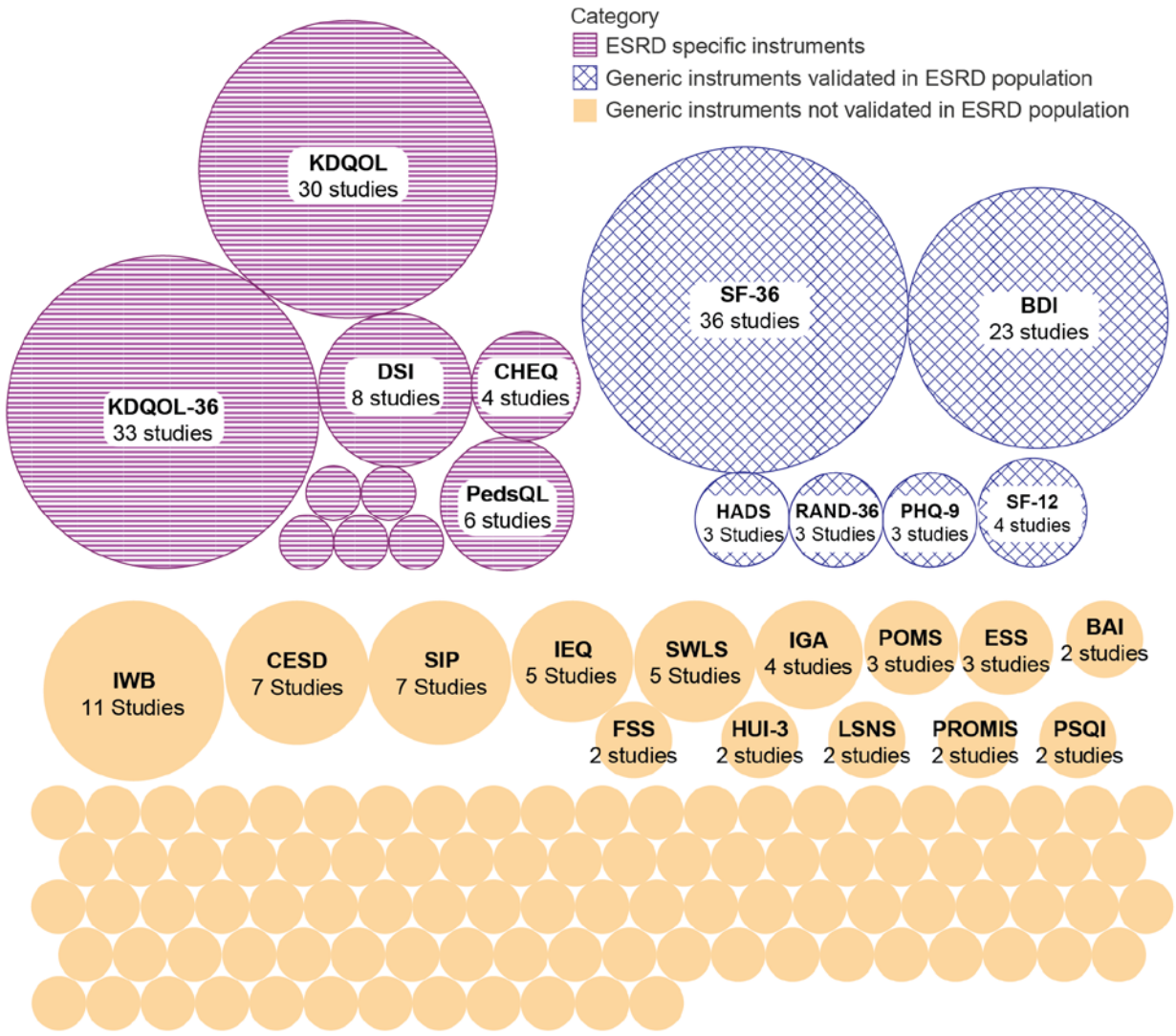
*White = white non-Hispanic; Black = black non-Hispanic. Details on other race/ethnicity available in Appendix F, Evidence Table T.

† See Appendix F, evidence table for details on race/ethnicity in the cohort studies.

Summary of Tools

One hundred twenty-five tools were described across the 165 included studies for KQ 4. Ten of these tools were designed and validated in ESRD populations treated by dialysis. Five of these tools were used in multiple studies. Six tools were designed in non-ESRD populations but validated in an ESRD population treated by dialysis (see Appendix F, Evidence Tables F6.1 and F6.2; Figure 12).

Figure 12. Tools used to measure quality of life or symptoms in individuals on dialysis.



* Unlabeled circles represent instruments used in only one study.

Epidemiologic Studies Depression Scale; CHEQ = CHOICE Health Experience Questionnaire; DSI = dialysis symptom index; ESRD = end-stage renal disease; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; HADS = hospital anxiety and depression score; HUI = health utilities index; IEQ = Illness Effects Questionnaire; IGA = index of general affect; IWB = index of wellbeing; KDQOL = kidney disease quality of life; Peds QL = pediatric quality of life scale; PHQ = physicians health questionnaire; POMS = Profile of Mood States; PRAS = Patient Related Anxiety Scale; PROMIS = Patient Reported Outcomes Measurement Information System; PSQI = Pittsburgh Sleep Quality Index; SF-36 = short forms 36; SIP = ; SWLS = satisfaction with life scale

The remaining tools were neither validated in nor designed for use in an ESRD population on dialysis, and were used in between one and 11 studies (Figure 12;Appendix F, Evidence Table F6.3) Appendix F Evidence Tables F6.1 through 6.3 include full lists of QOL and symptom tools used in the included studies and the domains they target.

Key Question 4a

What are the psychometric properties of instruments used to measure QOL in studies of people with ESRD treated by dialysis?

End-stage Renal Disease Specific Tools

Reliability

Reliability as Cronbach's alpha was reported on in five of the tools that were designed specifically for an ESRD population treated by dialysis: KDQOL, PedsQL, Dialysis Symptom Index (DSI), and CHOICE Health Experience Questionnaire (CHEQ). Cronbach's alpha is a measure of the reliability (i.e., internal consistency) of a set of scale or test items. In most instances, it was reported for the overall tool, the exception being CHEQ, as well as for multiple subscales for the tools. A Cronbach's alpha between 0.70 and 0.79 is considered good, between 0.80 and 0.89 is better, and above 0.90 is best.[85, 86] Most tools had a score of 0.70 (good) or higher with the following exceptions: KDQOL, appetite subscale (0.66); and the PedsQL parent ESRD total score (0.33) (see Appendix F, Evidence Table F7.1; Table 41).

Test retest reliability was reported on for DSI, and several subscales in the KDQOL. A test retest score of between 0.6 and 0.7 indicates questionable reliability, between 0.7 and 0.8 is acceptable, between 0.8 and 0.9 is good, and 0.9 or greater is excellent.[85] Most of the tools or subscales that reported test retest reliability reported a score of above 0.70. The KDQOL effects of kidney disease score was questionable (0.61), and one study of the DSI reported a less than questionable or poor test retest reliability (0.52),[87] but another reported acceptable reliability (0.80).[88] Many studies reported that the tools were reliable, but did not report data. Very little information was available from or about the five tools that were used in one study each (see Appendix F, Evidence Table F7.1; Table 41).

Validity

In the included studies, validity was reported in the following tools or their subscales: KDQOL, Pediatric Quality of Life (PedsQL), and DSI. Validity was stated but measures were not reported in the following tools and their subscales: KDQOL, Kidney Disease Quality of Life-36 (KDQOL-36), PedsQL, and DSI. Construct validity (i.e., the extent to which the measurements used actually test the hypothesis or theory they are measuring[89]) was only reported for the PedsQL scales; the analysis suggested that the two subscales had an acceptable fit. Content validity (i.e., the extent to which a measure represents a given construct) was improved through expert reviewers' determination of symptom relevance in the DSI scale. Relative validity, also referred to as relative precision or relative efficiency (which provides an appropriate quantitative index to compare the validity of PRO measures under the conditions in which such measures are typically used[90]) was reported in nine of the KDQOL subscales compared with the Short Form-36 (SF-36). Very little information was available from or about the five tools that were used in one study each (see Appendix F, Evidence Table F7.1; Table 41).

Table 41. Reported reliability and validity of quality of life and symptom measurement tools designed for use in an ESRD population treated by dialysis.

Tool: Subscale	Cronbach's alpha (Reliability)	Test retest (Reliability)	Stated Reliable*	Validity Measure	Stated valid†
KDQOL: Overall	0.7[91]	NR	NR	NR	NR
KDQOL: Dialysis staff encouragement	NR	0.82[92]	NR	NR	NR
KDQOL: Effects of kidney disease	NR	0.61[92]	NR	NR	NR
KDQOL: Cognitive function	0.72[93] 0.86[94]	NR	NR	Sensitivity, 52%; specificity, 82%[95] Relative validity of sub-scales; correlation with SF-36 scales[95]	NR
KDQOL: MCS	0.72 to 0.79[83]	NR	NR	NR	[83, 96]
KDQOL: PCS	0.72 to 0.79[83]	NR	NR	NR	[83, 96]
KDQOL: Burden/effects	0.88/0.86[97]	0.79/0.86[97]	NR	NR	NR
KDQOL: Symptoms/ problems	0.86[97]	0.85[97]	NR	NR	NR
KDQOL: Sleep	0.82[94]	NR	NR	Relative: validity of sub-scales; correlation with SF-36 scales[94]	NR
KDQOL: Pain	0.86[94]	NR	NR	Relative: validity of sub-scales; correlation with SF-36 scales[94]	NR
KDQOL: Psychological dependency	0.88[94]	NR	NR	Relative: validity of sub-scales; correlation with SF-36 scales[94]	NR
KDQOL: Dialysis related symptoms	0.69[94]	NR	NR	Relative: validity of sub-scales; correlation with SF-36 scales[94]	NR
KDQOL: Cardiopulmonary symptom	0.79[94]	NR	NR	Relative: validity of sub-scales; correlation with SF-36 scales[94]	NR
KDQOL: Energy	0.92[94]	NR	NR	Relative: validity of sub-scales; correlation with SF-36 scales[94]	NR
KDQOL: Cramps	0.73[94]	NR	NR	Relative: validity of sub-scales; correlation with SF-36 scales[94]	NR
KDQOL: Appetite	0.66[94]	NR	NR	Relative: validity of sub-scales; correlation with SF-36 scales[94]	NR
KDQOL: All other subscales	NR	NR	NR	NR	NR
KDQOL -36: Overall	0.84[98]	NR	NR	NR	[99-105]
KDQOL -36: Pain	0.83[93]	NR	NR	NR	NR
KDQOL -36: MCS	NR	NR	[106]	NR	[106]
KDQOL -36: PCS		NR	[106]		[106]
KDQOL -36: Effect of kidney disease	NR	NR	NR	NR	NR
KDQOL -36: Burden/effects	NR	NR	NR	NR	NR
KDQOL -36: Symptoms/ problems	NR	NR	NR	NR	NR

Tool: Subscale	Cronbach's alpha (Reliability)	Test retest (Reliability)	Stated Reliable*	Validity Measure	Stated valid†
KDQOL -36: All other subscales	NR	NR	NR	NR	NR
PedsQL: Overall	0.90[107]	NR	NR	NR	[108]
PedsQL: Child ESRD module	0.77[109]	NR	NR	Construct: confirmative factor analysis, child with ESRD self-report: comparative fit index 0.94, root mean squared error of approximation: 0.062, and non-normed fit index 0.93[109] "acceptable fit"	NR
PedsQL: Parent ESRD total score	0.33[109]	NR	NR	Construct: confirmative factor analysis for parent: comparative fit index, 0.95; mean squared error of approximation, 0.077, and non-normed fit index, 0.94[109] "acceptable fit"	NR
PedsQL: Children's depression inventory		NR	[110]	NR	[110]
PedsQL: Generic scale		NR	[110, 111]	NR	[111]
PedsQL: End-stage renal disease scale (3.0)	NR	NR	NR	NR	[111]
PedsQL: All other subscales	NR	NR	NR	NR	NR
DSI	0.86[112] 0.87[88]	0.80[88] 0.52[87]	NR	Content: noted good [113] Percent total agreement: 0.8+0.09 (SD); Kappa ranges from 0.06 to 0.9[113]	[88, 112]
CHEQ: Overall	>0.70[114]	NR	NR	NR	[114]
CHEQ: Sleep Quality	0.75[115, 116]	NR	NR	NR	NR
Home Dialysis Interview Schedule	NR	NR	NR	NR	NR
KDQ	NR	NR	[117]	NR	NR
RQLP	NR	NR	NR	Construct: has been validated with SF-36 and the SIP[118]	NR
unnamed validated questionnaire specifically designed for use in ESRD	NR	NR	[119]	NR	[119]
Home Dialysis Interview Schedule	NR	NR	NR	NR	NR
General Dialysis Treatment Stress Scale	NR	NR	NR	NR	NR

CHEQ = CHOICE Health Experience Questionnaire; KDQ = kidney disease quality; DSI = dialysis symptom index; ESRD = end-stage renal disease; KDQOL = Kidney Disease Quality of Life; KDQOL-36 =Kidney Disease Quality of Life, 36; MCS = mental composite summary; NR = not reported; PCS = physical composite summary; PedsQL = Pediatric Quality of Life; RQLP = Renal Quality of Life Profile

*Studies reporting that a tool was reliable but reporting no data

†Studies reporting that a tool was valid but reporting no data

Other Metrics

Feasibility, defined as minimal patient burden, was only reported in the PedsQL (child ESRD module and parent ESRD total score) and RAND-36. Minimal patient burden was evidenced by the minimal number of missing responses in the PedsQL.[109] In one study of RAND-36,

researchers used computer adapted testing to increase feasibility of this tool in their study population.[65] The following tool subscales evidenced usability, defined in terms of use in clinical practice: KDQOL, mental component summary, and physical component summary; KDQOL SF-36, mental component summary, physical component summary, burden/effect, and symptoms/problems (see Appendix F, Evidence Table F7.1 for details on these measures).

Tools Not Designed for an End-stage Renal Disease Population but Validated in an End-stage Renal Disease Population

Reliability as Cronbach's alpha was reported for three of the six tools not specifically developed for an ESRD population treated by dialysis but validated in this population. The scores were good for the SF-36 physical and mental composite summaries and better for BDI, non-somatic scale and the Short Form-12 (SF-12) mental composite summaries. Test retest reliability was reported in three subscales of one tool; this measure was excellent in the SF-36 mental composite summaries, and questionable for the SF-36 social functioning score. Many of these studies reported that the tools were reliable but did not report data (Table 42).

Validity was reported in terms of sensitivity and specificity for diagnosing depression in the BDI in one study.[120] Many studies reported that the tools were valid, but did not report data (see Appendix F, Evidence Table F7.2; Table 42).

Feasibility, as computer adapted testing, was only reported in the RAND-36 (physical functioning, physical health composite). Usability was not reported (see Appendix F, Evidence Table F7.2 for details on these measures).

Other Tools

Psychometric properties were rarely reported in included studies on the remaining tools. Two studies reported a Cronbach's alpha: one for the Center for Epidemiologic Studies Depression Scale (CES-D)[121] and one for the Multidimensional Fatigue Inventory-20 (MFI-20).[122] Two studies reported on test retest reliability: one for the Chronic Kidney Disease Quality of Life Tool (CKD-QOL)[97] and the other for the Quality of Wellbeing Scale.[123] Validity was reported in three studies: one as principal components analysis in the FSS,[122] one as construct validity in the Pittsburgh Sleep Quality Index (PSQI),[124] and one as a generic statement that the Satisfaction With Life Scale (SWLS) correlated with other QOL.[124]

Table 42. Reported reliability and validity of quality of life and symptom measurement tools not designed for use in an ESRD population treated by dialysis but noted as validated in an ESRD population treated by dialysis.

Tool: Subscale	Cronbach's alpha (Reliability)	Test retest (Reliability)	Stated Reliable*	Validity Measure	Stated valid†
SF-36: Overall	NR	NR	[125]	NR	[125]
SF-36: MCS	0.73[126]	0.9 or more[127]	NR	NR	[78, 112, 115, 128-132]
SF-36: PCS	0.78[126]	0.9 or more[127]	NR	NR	[72, 78, 112, 115, 128-133]
SF-36: Social functioning	NR	0.62[92]	NR	NR	NR
SF-36: Vitality	NR	NR	[115]	NR	[115]
SF-36: Bodily pain	NR	NR	[134]	NR	[112]
SF-36: All other subscales	NR	NR	NR	NR	NR
BDI: Overall	0.85[135]	NR	NR	Other construct: 92% Sensitivity and 80% specificity for diagnosing depression in HD patients[100]	NR
BDI: Non-somatic scale	0.86[135]	NR	NR	NR	[135]
RAND-36: Overall	NR	NR	[63]	NR	[57, 63, 136]
RAND-36: Physical functioning	NR	NR	NR	NR	[65]
RAND-36: Physical health composite	NR	NR	NR	NR	[65]
SF-12: Overall	NR	NR	NR	NR	NR
SF-12: MCS	0.87[97]	NR	NR	NR	NR
SF-12: PCS	0.84[97]	NR	NR	NR	NR
HADS: Overall	NR	NR	[137]	NR	[137]
HADS: Other subscales	NR	NR	NR	NR	NR
PHQ-9	NR	NR	NR	NR	NR

BDI = Beck Depression Inventory; HADS = Hospital Anxiety and Depression Scale; NR = not reported; PHQ-9 = Physicians Health Questionnaire, 9; SF-12 = Short form 12; SF-36 = Short form 36

*Studies reporting that a tool was reliable but reporting no data

†Studies reporting that a tool was valid but reporting no data

Key Question 4b

What is the minimal clinically important difference for instruments used to measure QOL in studies of people with ESRD treated by dialysis?

Minimal clinically important difference is the smallest amount an outcome must change to be meaningful to patients.[138] The minimal clinically important difference captures both the magnitude of the improvement and the value placed by the patients on the change. This measure was not reported often in the studies reporting on QOL and symptom measures in patients on dialysis. The PedsQL (score ranges from 0-100 in each module and in total score) reports an minimal clinically important difference of 4.36 in the ESRD child module and 4.5 in the parent ESRD total score.[107] Details about how minimal clinically important difference was calculated were not provided (see Appendix F, Evidence Tables F8.1 and F8.2).

More information was available in studies that reported on QOL and symptom measures that were not designed specifically for an ESRD population treated by dialysis but were validated in an ESRD population treated by dialysis. Some of the reported minimal clinically important differences for the SF-36 tool were conflicting. The overall minimal clinically important difference for the SF-36 was stated to be 10 points in a dialysis population in one study,[139] but additional information from a non-included article states that the minimal clinically important difference and interpretability are lacking in a mixed population.[140] Subscales for the SF-36 (score ranges 0-100 for each subscale) reported a minimal clinically important difference of between 2 and 5 for the physical and mental component summary scores.[141] This minimal clinically important difference was not derived in ESRD patients treated by dialysis, but was collected from other studies on the SF-36 in patients with osteoarthritis,[142] Crohn's disease,[143] temporomandibular joint and muscle disorder,[144] and general health disorders.[145] The SF-36 depression subscale does not report an minimal clinically important difference, but it does report that a 2-point change in score indicates that a patient was more likely to be depressed. Data was not provided about how this number was derived.[146] An additional study estimated an minimal clinically important difference of 5.7 in patients in chronic kidney disease stage 5 not on dialysis for the physical component summary score, based on differences in baseline functional status.[140] The RAND-36, used in the FHN study, was reported to have an minimal clinically important difference for the physical functioning and the physical health composite score of 3.[65] No information was provided about how this number was calculated.

A study on the BDI-II reported a change of 17.5 percent as an minimal clinically important difference.[147, 148] Additional searches did not identify minimal clinically important difference for the remaining tools and their subscales (see Appendix F, Evidence Tables F8.1 and F8.2).

Key Question 4c

How have instruments used to measure QOL in studies of people with ESRD treated by dialysis been validated?

None of the studies included for this KQ provided detailed information about the validation method. Therefore, we reviewed references provided by the studies about the validation method and extracted information about the validation method for both ESRD specific tools and tools not specifically designed for use in ESRD patients treated by dialysis but validated in this population. We limited this search to tools used in more than one study. Detailed information

about how tools were validated is available in Appendix F, Evidence Tables F9.1 and F9.2. All ESRD specific tools were validated in an ESRD (adult or pediatric), chronic kidney disease stage 4 or 5, or dialysis population. Through the review of cited articles and supplemental searching, we were able to identify validation methods in a dialysis population for four of the seven tools not designed in an ESRD population treated by dialysis but validated in an ESRD population treated by dialysis (see Appendix F, Evidence Tables F9.1 and F9.2; Table 43). Validation in general populations was available for the HADS and BDI-II measures. Comparisons were made between the general population and a dialysis population for the RAND-36 but specific methods were not provided (Table 43).

Validation methods for specific types of validity (e.g., construct, discriminant) were gathered from identified sources; we recorded the specific validity type as defined in the source articles. Validity (general and specific types) was assessed using a variety of methods (see Appendix F, Evidence Tables F9.1 and F9.2). General validity (as defined as "general validity, or not a defined type of validity in the included studies") was determined in seven of the tools by comparing specific tools with a gold standard or another tool, the "known groups" method, differences between categorical scores within a tool, and cut point validity.

Validation methods for construct validity (as identified in the source information) was determined in seven of the tools by factor analysis, comparison of overall scores with subscale scores, comparisons with a gold standard or other tool, the multitrait multimethod strategy, and the "known groups" method. Content validity was determined in one of the tools by expert consultation. Relative validity was determined in three of the tools by "known group" differences, unadjusted linear models, and F-statistic generation. Face validity was determined in one of the tools by comparing the tool with other questionnaires. Discriminant validity was determined in four of the tools by the "known groups" method, convergent multitrait multimethod analysis, range of effect sizes, agreement between measures, comparison with other validity measures such as convergent validity, and differences in scores between normal patients and subject patients. Other types of validity were reported, such as factorial, convergent, concurrent, and criterion validity (see Appendix F, Evidence Tables F9.1 and F9.2)

Key Question 4d

What is the impact of placebo effect in studies used to measure QOL in people with ESRD treated by dialysis and what study designs are needed to mitigate the impact?

None of the studies reported on placebo effect (see Appendix F, Evidence Table F10). Therefore, we reviewed all RCTs to evaluate whether they were randomized, placebo controlled, and double blind (neither the subjects nor the investigators were aware of treatment or placebo group allocation). We sought to estimate the placebo effect using the difference in difference method, comparing the change in the treatment arm with the change in the placebo arm during followup. Three of the RCTs were double blind placebo controlled. One study compared iron infusion with placebo,[149] and two studies compared l-carnitine to placebo.[117, 150] The study comparing iron infusion with placebo evaluated the intervention's impact on restless leg syndrome in dialysis patients, using a restless leg severity score (RLS). No placebo effect was detected; the placebo group showed no change in score and the intervention group

Table 43. Summary of validation method used for quality of life and symptom measurement tools designed for an ESRD population treated by dialysis and those not designed for an ESRD population treated by dialysis but validated in that population.

Tool: Subscale	Source	General/ not defined	Construct	Content	Relative	Face	Discriminant	Other	Population
KDQOL: Overall	Hays, 1994[151]	NR	X	NR	X	NR	NR	NR	ESRD
KDQOL: Symptoms/ problems; Effects of kidney disease	Rao, 2000[94]	NR	NR	NR	X	NR	NR	NR	ESRD
KDQOL: Cognitive function	Kurella, 2004[95]	X	NR	NR	NR	NR	NR	NR	ESRD and CKD
KDQOL-36: Overall	Gorodetskaya, 2005[94]	NR	NR	NR	NR	X	NR	NR	CKD 4 and 5
KDQOL-36: Overall and subscales	Ricardo, 2013[152]	NR	X	NR	NR	NR	NR	NR	Chronic renal insufficiency
KDQOL-36: Overall	Piepert, 2018[153]	NR	X	NR	NR	NR	NR	NR	Patients on dialysis
PedsQL: ESRD module of version 3.0	Goldstien, 2008	X	NR	NR	NR	NR	X	NR	Pediatric ESRD
DSI	Weisbord, 2004[113]	NR	NR	X	NR	NR	NR	NR	Dialysis population
CHEQ	Wu, 2001[114]	NR	X	NR	NR	NR	NR	Conver-gent: X	ESRD
SF-36: Physical activity	Johansen, 2001[154]	NR	NR	NR	NR	NR	NR	Study to establish validity in ESRD (PAR, PASE, HAP, and SF-36)	ESRD
SF-36: All scales	Diaz-Buxo, 2000[155]	X	NR	NR	NR	NR	NR	NR	PD and HD patients
BDI	Watnick, 2005[156]	X	NR	NR	NR	NR	NR	NR	Dialysis patients

Tool: Subscale	Source	General/ not defined	Construct	Content	Relative	Face	Discriminant	Other	Population
RAND-36	Hays, 2005[157]		Method not reported	NR	NR	NR	NR	NR	General with some comparisons in an ESRD population
SF-12: MCS, PCS, symptoms/problems, effects	Peipert, 2018[153]	X	NR	NR	NR	NR	NR	NR	ESRD
HADS	Bjelland, 2002[158]	NR	NR	NR	NR	NR	NR	Con-current: X	General Population
PHQ-9	Watnick, 2005[156]	X	NR	NR	NR	NR	NR	NR	Dialysis patients

BDI = Beck Depression Inventory; CHEQ = CHOICE Health Experience Questionnaire KDQ –Kidney disease quality; DSI = Dialysis Symptom index; ESRD = end-stage renal disease; HADS = Hospital Anxiety and Depression Scale; KDQOL = Kidney Disease Quality of Life; KDQOL-36; Kidney Disease Quality of Life, 36; MCS = mental composite summary; NR = not reported; PCS = physical composite summary; PedsQL = Pediatric Quality of Life; PHQ-9 = Physicians Health Questionnaire, 9; RQLP = Renal Quality of Life Profile; SF-12 = Short form 12; SF-36 = Short-form 36

showed improvement; however, there were concerns about whether blinding could be achieved when comparing iron infusions with placebo owing to distinct symptoms (e.g., sweet taste in mouth) that the patients experienced with iron infusions (see Appendix F, Evidence Table F9). One study compared l-carnitine supplementation with placebo, measuring four domains of the Kidney Disease Questionnaire (KDQ). Score improvement in all of the domains measured in the placebo group: total KDQ score (+0.29 points), physical symptoms (+0.68 points), fatigue (+0.24 points), and depression (+0.15 points). The KDQ is different from the KDQOL and no information was available on the minimal clinically important difference for the KDQOL. The other study comparing l-carnitine supplementation to placebo, measuring eight domains of the SF-36, showed score improvement in the placebo group in two of the domains: vitality (+1.70 points) and mental component summary (MCS; +2.2 points). No information was available for the minimal clinically important difference of the vitality subscale of the SF-36. A change in score of 2 to 5 points in the MCS is identified as an minimal clinically important difference.[141] The study reporting this minimal clinically important difference derived the range not from dialysis patients but from other populations.

Quality of Tools Specifically Designed for the End-stage Renal Disease Population Treated by Dialysis

We assessed the quality of the five most commonly used ESRD specific QOL and symptom measure tools using the COSMIN checklist.[23, 25]

We summarized our assessment of the five commonly used QOL and symptom measure tools designed for ESRD populations treated by dialysis that were identified in this report using the "worst counts" methods (see Table 44) and the median assessment score for each domain (see Table 45). Nine measurement properties were assessed. A tenth measurement property, cross cultural validity, was not assessed: in this review, we were mainly interested in the U.S. Medicare population and only assessed English language versions of the tools. We were not able to assess all domains for these tools owing to missing information.

For all of the tools, we assessed PROMs development, reliability, measurement of error, and responsiveness domains. PROM development, reliability, and measurement of error were assessed as poor for all of the tools.

Using the "worst counts" method (Table 44) reliability and measurement of error was poor in all tools. Responsiveness was assessed as good or very good in 4 tools, and poor in one. Internal consistency was assessed as very good in four tools, with insufficient information to assess this domain in the DSI tool. Content validity was assessed as poor in four tools, with insufficient information to assess this domain in the KDQOL-36 tool. Hypothesis testing was assessed in four tools and was very good in one, good in two, and poor in one. Criterion validity was assessed as good in one tool. Structural validity was not assessed. Overall, none of the tools received a good or very good assessment for all of the measurement properties using this method.

We also assessed methodological quality by taking the median assessment rating of applicable scores for each domain (Table 45). We report the differences in scores here: The PROM development assessment changed from poor to good or very good in all of the tools; internal consistency did not change; reliability changed from poor to good in three tools (DSI, KDQOL-36, and PedsQL); Measurement of error changed from poor to good in one tool (DSI); content validity did not change; hypothesis testingchanged from poor to good in one tool

(KDQOL), and good to very good in another (DSI); criterion validity did not change int eh tool assessed; and responsiveness changed from good to very good for one tool (DSI)

Table 44. COSMIN assessment of the quality of the most commonly used ESRD specific quality of life and symptom measure tools using the "worst counts" method.*†

Instrument	PROM develop-ment	Internal consistency	Reliability	Measurement of error	Content validity	Structural validity	Hypothesis testing	Criterion validity	Respon-siveness
KDQOL[151]	Poor	Very Good	Poor	Poor	Poor	INA	Poor	INA	Poor
CHEQ[159, 160]	Poor	Very Good ‡	Poor	Poor	Poor	INA	Good ‖	INA	Very Good
DSI[87, 113]	Poor	INA	Poor	Poor	Poor**	INA	Good	INA	Good
KDQOL-36[153]	INA	Very Good	Poor	Poor	INA	INA	Very Good	INA	Very Good
PedsQL[109]	Poor	Very Good	Poor	Poor	Poor	INA	INA	Good	Very Good

CHEQ = CHOICE Health Experience Questionnaire; DSI = Dialysis Symptom Index; INA = information not available to assess this domain; KDQOL = Kidney Disease Quality of Life; KDQOL-36 = Kidney Disease Quality of Life, 36 item; PedsQL = Pediatric Quality of Life Inventory; PROM = patient reported outcome measure
*See the glossary for definitions; ‡assessed by Aiyegbusi as poor; ‖ assessed by Aiyegbusi as fair; ** assessed by Aiyegbusi as fair

Table 45. COSMIN assessment of the quality of the most commonly used ESRD specific quality of life and symptom measure tools using the median assessment score for each domain *†

Instrument	PROM develop-ment	Internal consistency	Reliability	Measurement of error	Content validity	Structural validity	Hypothesis testing	Criterion validity	Respon-siveness
KDQOL[151]	Very Good	Very Good	Poor	Poor	Poor	INA	Good	INA	Poor
CHEQ[159, 160]	Good	Very Good ‡	Poor	Poor	Poor	INA	Good ‖	INA	Very Good
DSI[87, 113]	Good	INA	Good	Good	Poor**	INA	Very Good	INA	Very Good
KDQOL-36[153]	INA	Very Good	Good	Poor	INA	INA	Very Good	INA	Very Good
PedsQL[109]	Very Good	Go Very Good od	Good	Poor	Poor	INA	INA	Good	Very Good

CHEQ = CHOICE Health Experience Questionnaire; DSI = Dialysis Symptom Index; INA = information not available to assess this domain; KDQOL = Kidney Disease Quality of Life; KDQOL-36 = Kidney Disease Quality of Life, 36 item; PedsQL = Pediatric Quality of Life Inventory; PROM = patient reported outcome measure
*See the glossary for definitions; ‡assessed by Aiyegbusi as poor; ‖ assessed by Aiyegbusi as fair; ** assessed by Aiyegbusi as fair

domains assessed. PedsQL received a good assessment for five of the seven domains assessed. KDQOL-36 received a good assessment for four of the five domains assessed.

A systematic review published in 2017[161] assessed a number of QOL and symptom measure tools in adult patients with kidney disease using a previous version of the COSMIN tool.[7] We reviewed this paper to compare their COSMIN assessments with those we completed. This review assessed all of the tools we included, with the exception of the PedsQL. Since the previous systematic review authors were only looking at adult outcomes, we were not able to compare an assessment for PedsQL. Aiyegbusi, et al. assessed the KDQOL instrument using a different reference article focusing on predialysis patients and assessed the KDQOL-36 using seven articles that did not focus solely on a dialysis population or an English language population.[161] We were able to compare the Aiyegbusi assessment to our assessments for the CHEQ and the DSI.

Our team and Aiyegbusi, et al. assessed the CHEQ tool using the Wu, et al. 2001 paper that discussed the tool.[159] In addition, our team assessed Wu, 2004;[160] this assessment did not impact

the overall COSMIN assessment. The differences are most likely due to using different versions of the COSMIN tool.

When using the “worst scores” method, our assessments differed from the Aiyegbusi assessments. When using the median assessment rating, our assessments were more favorable than those conducted by Aiyegbusi.

Discussion

Key Findings

We conducted a systematic review of the literature to assess the effect of more frequent or longer hemodialysis on clinical outcomes and QOL in ESRD patients and to assess the QOL instruments used in U.S. studies of patients with ESRD treated by dialysis. We defined usual care as thrice-weekly hemodialysis with a total treatment time of less than 12 hours per week. We defined longer hemodialysis as thrice weekly hemodialysis with treatment time greater than or equal to 12 hours per week, frequent hemodialysis as four or more treatments per week with total treatment time less than 16 hours per week, and frequent and longer hemodialysis as four or more treatments per week and treatment time greater than or equal to 16 hours per week.

We abstracted data from available studies and extrapolated from these studies to the U.S. Medicare-eligible ESRD population when possible. For the studies on frequent and longer hemodialysis, we abstracted 17 studies (published in 39 articles). Of the 17 studies, 3 were RCTs, 1 was a non-randomized clinical trial, and 13 were observational studies. Compared to the U.S. Medicare population receiving hemodialysis, the study populations were younger, more likely to be white, more likely to receive hemodialysis at home, and had lower mortality rates (see Tables 46 and 47).

Compared to usual care, low level of evidence suggested that more frequent hemodialysis and more frequent and longer hemodialysis improved a number of blood pressure-related parameters (including systolic blood pressure, number of antihypertensive medications, ultrafiltration rate, and intradialytic hypotension). It lowered serum phosphorus and oral phosphorus binder dose but increased vascular access complications. For more frequent hemodialysis, but not for more frequent and longer hemodialysis, low level of evidence suggested reduction in the risk of death and lowering of LV mass, compared to usual care. More frequent and longer hemodialysis was associated with a faster decline in residual kidney function. For longer hemodialysis without increased frequency, the evidence was insufficient to determine the effects on any of the outcomes or harms.

We also conducted an in-depth evaluation of the instruments that have been used to measure QOL in people with ESRD treated with dialysis (hemodialysis or peritoneal dialysis). We abstracted 165 studies (23 RCTs and 142 cohort studies) published in 185 articles) that reported using 123 different QOL and symptom measure tools. Of these 125 tools, 10 were designed and validated in ESRD populations, and six were designed in non-ESRD populations but validated in the ESRD population. The most widely used tools that were both designed for and validated in an ESRD population were the KDQOL-36, KDQOL, DSI, CHEQ, and PedsQL. Five additional tools were designed for the ESRD population but were only used in one of the studies. We also identified seven tools that were not specifically designed for but were validated in an ESRD population. The most commonly cited were the SF-36 and the BDI. Reliability and validity were measured and reported for both the ESRD specific tools and tools not ESRD specific but validated in this population. Often these metrics were calculated in subscales, and not for the entire tool. The studies generally did not report on the minimal clinically important difference in QOL or symptom scores, defined as the smallest amount that an outcome must change to be meaningful to the patients. The studies also did not report on placebo effects with instrument administration.

Table 46. Description of applicability of evidence on KQs 1-3

PICOT	Description
Population	Included patients were younger and more likely to be white than the U.S. hemodialysis population.
Intervention	The more frequent hemodialysis intervention and longer hemodialysis treatments were provided using incenter hemodialysis systems, which should be comparable to contemporary care. The longer hemodialysis treatments and the more frequent and longer hemodialysis treatments were provided hemodialysis systems that are different from what is being used most often in contemporary practice (NxStage).
Comparators	Usual care hemodialysis (thrice weekly for less than or equal to 4 hours per treatment) is comparable to current clinical practice.
Outcomes	Except for the pragmatic TiME trial, the observed mortality rates in the control groups of the clinical trials and most observational studies were lower than the U.S. hemodialysis population.
Setting	In the US, 98% of the patients receiving hemodialysis are treated in-center. The FHN Daily trial, the TiME trial, and the Ayus study included incenter patients. The FHN Nocturnal trial included only patients receiving hemodialysis at home.

ESRD = end-stage renal disease; KQ = key question; QOL = quality of life; TiME = Time to Reduce Mortality in End-Stage Renal Disease Trial

Table 47. Description of applicability of evidence on KQ 4

PICOT	Description
Population	Included patients were not comparable to the USRDS hemodialysis population.
Intervention	Any intervention was allowed if the population was on dialysis and their quality of life or symptoms were measured using patient-reported outcome measures.
Comparators	No comparators
Outcomes	Studies reported on at least one quality of life or symptom measure (as reported by the patient)
Setting	Non-institutionalized individuals (no inpatient)

KQ = key question

For studies evaluating the effects of hemodialysis frequency and duration, the strength of evidence was low, based on one RCT, that more frequent hemodialysis led to improvement in several domains of QOL assessed using RAND-36, including the physical health composite score, general health, physical functioning, mental health composite score, emotional wellbeing, and energy/fatigue. Compared to usual care, the strength of evidence was low that more frequent hemodialysis and more frequent and longer hemodialysis shortened time to recovery after completing hemodialysis treatment. The minimal clinically important difference and placebo effect associated with these QOL metrics are unknown.

Limitations of Evidence

Clinical Outcomes

We defined usual care as thrice-weekly hemodialysis with a total treatment time of less than 12 hours per week, which corresponds to less than 4 hours per treatment. This categorization, developed with input from the technical expert panel and key informants, is consistent with the delivered hemodialysis treatment duration in the U.S. In the US, 98 percent of the patients receiving hemodialysis are treated in-center thrice-weekly with a median treatment time of 3 hours and 40 minutes (25^{th} percentile, 3 hours and 28 minutes; 75^{th} percentile, 4 hours).[162] The

FHN Daily trial, the TiME trial, and the Ayus study included in-center patients. For studies that included 4 or more treatments per week, the frequency of treatments varied based on the location of dialysis treatment (in-center versus home) and the type of hemodialysis machine in use. The FHN Nocturnal trial included only patients receiving hemodialysis at home.

Different hemodialysis systems are used to provide hemodialysis. In general, the hemodialysis machines used in-center provide greater dialyzer urea clearance per unit time than the most commonly used home hemodialysis system in the U.S. manufactured by NxStage.8, 163 Volume clearance per unit time is similar across the different hemodialysis systems. Among the RCTs, the pragmatic TiME trial, the FHN Daily trial, and the Ayus study were conducted incenter and presumably used the incenter hemodialysis systems that are part of standard clinical practice. The FHN Nocturnal trial of home hemodialysis did not use the NxStage system (personal communication: Dr. M Rocco; 12 October 2019), which is the most common way of delivering more frequent home hemodialysis and nocturnal hemodialysis in the US. Due to the NxStage dialyzer's lower urea clearance per unit time compared to incenter hemodialysis systems, frequent or longer hemodialysis treatment time is needed to achieve the same weekly hemodialysis urea clearance that can be achieved by thrice-weekly incenter hemodialysis. Urea clearance is used as a surrogate for clearance of other uremic toxins with the assumption that all of the non-urea solutes have the same production, distribution in body compartments, and removal kinetics as urea.164-166 Most of the non-urea solutes are unknown, and for the few known non-urea solutes such as p-cresol sulfate, these assumptions are not valid, and their removal kinetics by different hemodialysis systems have not been quantified. Therefore, it is not possible to extrapolate the non-urea solute removal achieved by the six times per week schedule used for the FHN Daily and Nocturnal trials to the NxStage System.

Volume overload is a significant contributor to hypertension and LV hypertrophy in patients receiving hemodialysis. Volume removal with each hemodialysis treatment is a function of the treatment time and patient characteristics that contribute to intradialytic hypotension as opposed to the type of dialyzer. Therefore, the effects of volume removal can be extrapolated from the FHN Daily and Nocturnal trials to home hemodialysis treatments using the NxStage System. These effects include both beneficial effects such as control of blood pressure and regression of LV mass, and harmful effects such as loss of residual kidney function and vascular access complications. Importantly, we defined frequent or longer hemodialysis treatments based on either a consistent prescription in observational studies or randomized intervention in clinical trials.

In the FHN Daily and Nocturnal trials, the predialysis systolic blood pressure and antihypertensive medication use were lower in the active treatment groups. However, the intervention was not blinded, blood pressure measurements were not standardized, and antihypertensive medication use was based on self-report, all of which can bias these results. Bias in blood pressure measurement in the absence of blinding is well-described. Bias in blood pressure measurement and other factors could also influence self-reported antihypertensive medication use. Blood pressure measurements in routine hemodialysis clinical practice ("usual" blood pressure) are not standardized and most automated blood pressure devices have not been validated in hemodialysis patients. These factors introduce measurement errors in blood pressure. Additionally, predialysis and postdialysis blood pressures are imprecise estimates of blood pressure between hemodialysis treatments.[12] The blood pressure measurement conditions during the FHN RCTs may be different from routine clinical practice in both incenter and home hemodialysis settings. The FHN investigators acknowledged this limitation stating that

"compared with subjects on conventional [hemodialysis], subjects on incenter daily [hemodialysis] may be reminded to take medications, have blood pressure assessments, and receive nutritional counseling more often.[68]"

The mortality rate of the control group in hemodialysis clinical trials could be considered a metric to assess if the trial populations are similar to the U.S. hemodialysis population. The mortality rate for the U.S. hemodialysis population in 2016 was 16.6 per 100 person-years. In contrast, during the 12-month trial phase of FHN, the mortality in the control groups was markedly lower, with nine deaths in the Daily trial (overall mortality rate, 7.5%) and one death in the Nocturnal trial (overall mortality rate, 2.4%). During the extended followup of the FHN trials, the mortality rate for the usual care group continued to be much lower than the U.S. hemodialysis population, 8.2 per 100 person-years for the Daily trial and 3.3 per 100 person-years for the Nocturnal trial. The low mortality rate in the control group suggests either selection bias with inclusion of a trial population much healthier than the U.S. hemodialysis population or the effect of attention during the clinical trial. It also highlights the marked heterogeneity in survival of the U.S. hemodialysis patients and the inherent difficulty faced by clinicians in identifying patients that match the population included in the FHN Daily trial who may benefit from more frequent hemodialysis. The FHN investigators were cautious in their interpretation of the results. They noted that "relative to the entire North American hemodialysis population, participants in the FHN Daily Trial were younger, had longer hemodialysis vintage, and by design, had low levels of residual kidney function; therefore, these results may not be generalizable to all patients." The FHN investigators also indicated that "these results should not be extrapolated to other methods of daily hemodialysis that do not provide the hours of hemodialysis time or solute clearance achieved in the FHN Daily Trial", and that "frequent hemodialysis may benefit selected patients with ESRD".

The primary clinical benefit of the FHN Daily trial appeared to be from better volume control, which contributed to better blood pressure control and lower LV mass. The three extra hemodialysis treatments in the intervention group compared to the thrice weekly group contributed to an average of 1.6 L higher weekly fluid removal. By design, the FHN trial excluded participants with significant residual kidney function. As a result, at baseline, 66 percent of the FHN Daily trial participants were anuric and 84 percent had been on hemodialysis for more than two years. This trial population is very different from patients starting hemodialysis, the majority of whom have significant amounts of residual kidney function and are not anuric. Presence of residual kidney function and daily urine volume of even 250 mL per day can provide 1.7 L per week of extra volume clearance compared to anuria. The FHN results are, therefore, mostly applicable to prevalent hemodialysis patients with anuria and may not be relevant to incident hemodialysis patients with significant residual kidney function.

The pragmatic TiME trial targeted incident incenter hemodialysis patients. In the TiME trial, the control group's mortality rate, 17.4 per 100 person-years, was similar to the mortality rate in the U.S. hemodialysis population. The results of the TiME trial are, therefore, applicable to the U.S. incident hemodialysis population. However, the trial was terminated early due to failure to achieve separation in treatment time between the control and intervention groups. So, it remains unknown whether the trial intervention, hemodialysis duration of 4 hours and 15 minutes (45 minutes longer per treatment than usual care) delivered thrice weekly, is effective in reducing mortality in incident hemodialysis patients.

The 13 observational studies included 2,465 patients treated with frequent hemodialysis (home hemodialysis, 92%), 32,871 patients treated with longer hemodialysis (all incenter

hemodialysis), and 454 patients treated with hemodialysis that was both more frequent and longer (100% home nocturnal hemodialysis). In comparison, 98 percent of all U.S. hemodialysis patients are treated with incenter hemodialysis, limiting applicability of these studies. The major analytic issues in the analysis of the observational studies relate to unmeasured confounders at baseline and time-varying confounding and mediation during followup. Instrumental variable analysis,[167] a method to account for unmeasured confounders, was not used in any of the observational studies. The study by Miller used time-dependent Cox models, which could assess the effects of time-varying predictors but not mediation.[41] The study by Brunelli, with a population overlapping with the Miller Study, did use marginal structural models, which account for time-varying confounding affected by prior mediation. These authors found different associations when using marginal structural models (HR comparing shorter hemodialysis duration to longer hemodialysis duration, 1.42; 95% CI, 1.24-1.62) versus time updated multivariable adjusted models (HR for the same comparison 1.00, 95% CI, 0.87-1.14).[43] As discussed above, there are differences between the hemodialysis systems in use at home. Brunelli and colleagues,[33] compared 1-year outcomes for patients treated at home with either the NxStage System One or Fresenius 2008K@home system. The 2008K@home system is similar to the hemodialysis systems used for incenter hemodialysis. The treatment frequency was higher for NxStage users compared to 2008K@home users, reflecting the lower dialyzer urea clearance per unit time. No differences were observed in hospitalizations or other routine laboratory parameters over one year, suggesting that, at least over a year, the two systems provided similar clearance of the clinically measured solutes (urea, phosphorus, potassium, and calcium).

The mortality rate of the matched comparison population in the observational studies varied. In the study by Weinhandl,[38] comparing home hemodialysis patients using NxStage system, the matched incenter hemodialysis population had a mortality rate of 12.7 per 100 person-years which is lower than the mortality rate for the U.S. hemodialysis population.[38] In other observational studies, the mortality rate per 100 person-years for the matched control population was higher; 13.9 in the study by Nesrallah,[168] 14.7 in the study by Rivara,[40] and 17.8 in the study by Mathew.[32] These different mortality rates suggest that the control groups across these studies may not be comparable.

An important consideration in comparing the effects of hemodialysis frequency and duration is the location of hemodialysis delivery, specifically home hemodialysis. Patients selecting home hemodialysis, and their providers, may be very different from patients receiving incenter hemodialysis. Such differences can contribute to residual confounding in observational analyses when comparing patients receiving home hemodialysis to patients selected or matched on key variables from an incenter hemodialysis population. In the FHN Nocturnal trial, patients in the control and intervention groups received hemodialysis at home and the results may not be applicable to patients receiving incenter hemodialysis. The factors contributing to patients' selecting home hemodialysis were not the focus of our study but are an essential consideration as the U.S. nephrology community prepares for the challenge of increasing home hemodialysis set forth by the Advancing American Kidney Health initiative.

This systematic review was designed to synthesize information of relevance to the U.S. hemodialysis population. The U.S. hemodialysis population is significantly different from the dialysis population in the rest of the developed countries.[169-172] These differences are attributed to the underlying prevalence of comorbidities such as diabetes and cardiovascular disease,[169-172] hemodialysis modality,[172] predialysis access to health care as reflected by the type of vascular access in use at the time of hemodialysis initiation,[173] delivered hemodialysis dose (urea

clearance) and treatment time,[174] treatment adherence,[175] provision of nutrition during hemodialysis,[176, 177] nurse-to-patient ratios, and direct physician supervision of hemodialysis treatments.[169] These systematic differences in the patient populations compound the difficulties in the interpretation of trial results and judging their applicability to the U.S. hemodialysis population. As a result, we restricted our review to the studies that were either conducted entirely in the U.S. or those where the majority of recruited patients were from the U.S. Some of the non-U.S. studies excluded from this systematic review provide evidence supportive of our findings. For example, in a pilot study, Culleton et al. randomized 52 patients from two Canadian university centers to either nocturnal hemodialysis treatments provided six times per week or usual care hemodialysis treatments provided three times per week.[178] Similar to the FHN trials, frequent and longer hemodialysis lowered left ventricular mass and blood pressure but had did not improve overall quality of life. More recently, a Clinical Trial of Intensive Dialysis (ACTIVE),[179] randomized 200 patients from Australia, China, Canada, and New Zealand to standard or extended hemodialysis (at least 24 hours per week). There were no differences in the quality of life between the two groups. However, unlike FHN, blood pressure was similar between the groups, and in a subgroup of 95 patients with left ventricular mass measured by MRI, longer hemodialysis did not lower left ventricular mass. The quality of life findings from the ACTIVE trial are similar to the findings from our systematic review. The inconsistency of the effects of these interventions on blood pressure and left ventricular mass, comparing the Culleton trial to the ACTIVE trial, supports the designation of the low strength of evidence in our systematic review.

Quality of Life Instruments

For tools designed and validated in the ESRD population, a minimal clinically important difference was reported only for PedsQL (ESRD child module, and ESRD total score). For tools not specifically designed for but validated in an ESRD population, the SF-36 (overall and some subscales), and BDI-II reported minimal clinically important difference. Details on how it was calculated or its validity in the ESRD population was not reported in the papers or their referenced citations. We also evaluated the studies to assess if placebo effect had been calculated, requiring a double-blind study design. Such a design was only reported in one study that used KDQ and one study that used SF-36 and showed improvement in two of its domains with placebo, vitality (+1.70 points), and mental component summary (MCS; +2.2 points). However, minimal clinically important difference is unknown for the vitality subscale and for MCS, it is reported as 2 to 5, but this information is from non-dialysis populations.

For studies evaluating the effects of hemodialysis frequency, the strength of evidence was low, from one RCT, the FHN Daily trial, that more frequent hemodialysis led to improvement in QOL scores, assessed using RAND-36, a QOL tool developed in a general population and validated in the dialysis population. The scores for the domains (absolute improvement) that were statistically significant were as follows: physical health composite score (+3.2), general health, physical functioning (+2.9), mental health composite (+3.5), emotional wellbeing (+5.5), and energy/fatigue (+8.3). The minimal clinically important difference and placebo effect of this metric are not known.

Change in QOL score during a trial could be due to a number of factors beside the intervention such as the effects of attention, survey burden, and the interviewer administering the survey. Additionally, the scores may change over time as sicker people with higher symptom burden die, healthier people with lower symptom burden get kidney transplants, and transplant

ineligible individuals or those with long waiting times get sicker with increase in symptoms. These factors were not addressed in the reviewed studies.

It is also important to distinguish between factors contributing to QOL. Many factors are related to mental health and social determinants of health that contribute to kidney failure or result from consequences of kidney failure. Among the factors directly related to hemodialysis, some could be related to hemodialysis delivery infrastructure, such as the hemodialysis facility and the hemodialysis clinic staff's interpersonal skills. Dialysis itself can only change QOL by safely and effectively enhancing removal of fluid and uremic toxins that cause uremic symptoms such as fatigue, anorexia, nausea, vomiting, pruritus, impaired cognition, sleep disturbances, and restless legs. The change in QOL is reflective in the net effect of all these factors and even complete restoration of kidney function, such as by kidney transplantation, may not address many of the non-kidney clearance related factors that contribute to QOL.

Tool nomenclature can be confusing. Tools have evolved over time and changed names, with minor differences between them, For example: the SF-36 and RAND-36 QOL tools contain the same set of questions. The difference in these two tools is the algorithm used for scoring the pain and general health subscales.[22] While the scoring is highly correlated we reported on them separately based on how the tool was identified in the included article. Additionally, the KDQOL is not a single instrument. The original long form included 134 survey items with subsequent short forms (KDQOL-SF 1.3), and then an even shorter short form (KDQOL-36). The latter yields scores for the SF-12 physical and mental health summary scores plus the burden of kidney disease, symptoms/problems of kidney disease, and effects of kidney disease.[180]

Although many of the QOL tools were validated quite some time ago, there have not been any major scientific breakthroughs in our understanding of the mechanisms of symptoms experienced by patients with ESRD or technological breakthroughs in hemodialysis technology. Indeed, the prevalence of many symptoms in patients with ESRD has not changed much over the past 15 years,[181] so the validated instruments remain relevant to the contemporary dialysis population.

Limitations of the Systematic Review Process

We limited our search to English language articles indexed by PubMed and may have missed relevant, non-English published literature. As our review was limited to published literature, it was therefore subject to publication or selective outcome reporting bias (i.e., where the authors do not publish negative results). Throughout the report, we try to focus on the studies that have the lowest risk of bias, such as RCTs, regardless of sample size. For KQs 1, 2, and 3, we excluded studies conducted before 2005 as that year marks the start of use of NxStage hemodialysis system in the U.S. and the rise of frequent home hemodialysis. For KQ4, we did not limit our search by year of publication. To maintain applicability to the U.S. hemodialysis population, we included international studies only if the U.S. data were separately reported or if the study population was predominantly U.S. based.

Across all outcomes addressed in key questions 2, 3, and the combined 2 and 3, the strength of evidence was assessed as either low or insufficient. As described in the Methods section of this report, we followed AHRQ guidance when we assessed the strength of evidence.[182] Following these guidelines reduces bias in the overall strength of evidence. Several factors impacted these strength of evidence assessments. A primary contributing factor lowering strength of evidence assessments was important study limitations. None of the RCTs had low study limitations, with judgments ranging from "some concerns" to "high" as evaluated using the

Cochrane Risk of Bias-2 tool.[183] Additionally, none of the cohort studies were judged to have low study limitations. Further, the available evidence was often imprecise or inconsistent across studies.

This review is not intended as a guideline or guidance document which includes evaluation of strength of evidence and opinions of leading content area experts. Guidelines such as those created by Kidney Diseases Improving Global Outcomes (KDIGO),[184] include a combination of assessment of the strength of the evidence of the published studies and expert opinion, contributing to their recommendations.

Research Recommendations

Our review highlights that the U.S. hemodialysis population is extremely heterogeneous and many of the published studies have limited applicability. The RCTs completed in the U.S. population also highlight the difficulties in recruiting trial populations that are generalizable and implementing pragmatic trial interventions. To our knowledge, there are no ongoing U.S. studies evaluating the specific interventions that were assessed in this report.

The following are some recommendations to fill evidence gaps and guide future research.

New clinical trials: Clinical trials in the hemodialysis population are difficult for a variety of reasons. Improving methods for screening and recruitment, such as the use of teleconsent, may facilitate enrollment. Clinical trials are needed to rigorously evaluate the effect of different hemodialysis duration, frequency, and patterns (such as every other day hemodialysis) on clinical outcomes, novel surrogate markers of hemodialysis clearance (for example, protein-bound uremic solutes), and ESRD specific symptoms. Targeted efforts to enhance uremic toxin discovery and clinical trials to mitigate the effects of these toxins are also needed. Most hemodialysis trials excluded patients initiating hemodialysis and those with residual kidney function; trials are needed in this population. Clinical trials are also needed to evaluate volume control strategies. Implementation studies are needed to standardize measurement and reporting of blood pressure measurements in hemodialysis patients.

QOL and symptoms from ESRD: Rigorous studies of QOL instruments are needed to provide information on the validity, reliability, minimal clinically important difference, and placebo effects for QOL outcomes. Design considerations for such studies include: eliminating interviewer bias, standardizing survey administration, using a double-blind study design, incorporating multiple measures of QOL and symptoms, and obtaining global assessments of health. The direct benefits of dialysis relate to removal of volume and uremic toxins, but the QOL and symptom instruments generally evaluate multiple symptoms, some of which may not be related to the accumulation of uremic toxins or volume overload in ESRD. It will be important to develop validated scores for ESRD specific symptoms and their burden, as opposed to all symptoms in patients treated with dialysis. Such scores will be invaluable in assessing the effect of novel therapies proposed as part of the KidneyX and Advancing American Kidney Health initiatives.[185]

Observational Studies:

Clinical trial applicability: Developing methods to identify patients with characteristics and prognosis similar to the patients in FHN trials will enhance trial applicability.

Econometrics: Modeling to identify the financial impacts of different hemodialysis treatment strategies will provide insight into decisions and have policy implications.

Rigorous methods for the analysis of observational data: Uncontrolled confounding, mediation, and selection bias were common in studies evaluated for this report. Studies could be strengthened by making greater use of causal methodology such as marginal structural models, and those addressing uncontrolled confounding such as instrumental variables. These methods can also be used to assess further the harm signal observed in the FHN Nocturnal trial. The availability of pooled treatment level data from multiple hemodialysis providers can facilitate future analyses.

Conclusions

The overall strength of evidence is low that selected prevalent hemodialysis patients with low expected mortality and minimal residual kidney function may benefit from more frequent hemodialysis with a lower risk of death, lowering of blood pressure, reduction in antihypertensive medication use, and lowering of LV mass. However, these benefits need to be balanced with an increased risk of vascular access complications and uncertainty about the effect on total mortality.

Many tools have been used to assess QOL and symptoms in the dialysis population, but more research is needed to fill in essential gaps in our understanding of the validity of the tools.

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List of Acronyms

/min	Per minute
3MS	Modified Mini-Mental State Examination
3x	3 times
3x/week	3 times per week
3x/wk	3 times per week
3xwk	3 times per week
6x	6 times
6x/week	6 times per week
6x/wk	6 times per week
6xwk	6 times per week
ACOVA	Analysis of covariance
ADAT	Appetite and Diet Assessment Tool
ADL	Activities of Daily Living
AHRQ	Agency for Healthcare Research and Quality
AI/AN	American Indian/Native American
AIDS	Acquired Immunodeficiency Syndrome
ANCOVA	Analysis of covariance
API	Asian/Pacific Islander
ArMORR	Accelerated Mortality on Renal Replacement cohort
ARPD	American Registry for Pregnancy in Dialysis Patients
BAI	Beck's Anxiety Inventory
BDI	Beck's Depression Inventory
BDI-II	Beck's Depression Inventory-II
Black	Black, non-Hispanic
BMI	Body Mass Index
BNH	Black non-Hispanic
BP	Blood pressure
BSA	Body surface area
CBC	Complete blood count
CDI	Cognitive Depression Index
CES-D	Center for Epidemiologic Studies Depression Scale
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CHAMPS	Community Healthy Activities Model Program for Seniors
CHD	Conventional hemodialysis
CHEQ	CHOICE Health Experience Questionnaire
CHF	Congestive Heart Failure
CHOICE	Choices for Healthy Outcomes in Caring for End-Stage Renal Disease Cohort Study
CHQPF50	Child Health Questionnaire Parent Form
CI	Confidence interval
CKD	Chronic kidney disease
CKD-QOL	Chronic Kidney Disease Quality of Life Tool

COSMIN	COnsensus-based Standards for the selection of health status Measurement Instruments
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	diastolic blood pressure
DHHD	Daily home hemodialysis
DOPPS	The Dialysis Outcomes and Practice Patterns Study
DSI	dialysis symptom index
ECF	Extracellular fluid
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EHC program	Effective Health Care Program
eKt/V	Equilibrated Kt/V (urea clearance)
EPC	Evidence Based Practice Center
EPO	Erythropoietin
ERI	Effort-Reward Imbalance Questionnaire
ESA	Erythropoietin-stimulating agents
ESAS	Edmonton Symptom Assessment System
ESRD	end-stage renal disease
ESS	Epworth Sleepiness Scale
ET	Evidence table
F/u	followup
FAAM	Foot and Ankle Ability Measure
FACIT-Sp	Functional Assessment of Chronic Illness Therapy—Spirituality Scale
FHN	Frequent Hemodialysis Network trials
FMCNA	Fresenius Medical Care North America
FREEDOM	Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements Study
FSFI	Female Sexual Function Index
FSS	Fatigue Severity Scale
FT3	Free triiodothyronine (T3)
FT4	Free thyroxine (T4)
g	grams
g/dl	grams per deciliter
g/m^2	grams per meters squared
g/ml	grams per milliliter
GAD-7	Generalized Anxiety Disorder 7-item Scale
GFR	Glomerular filtration rate
h	Hours
HADS	Hospital Anxiety and Depression scale
HAM-D	Hamilton Depression Rating Scale
HAP	Human Activity Profile
HD	Hemodialysis
HEMO	The Hemodialysis Study
Hgb	Hemoglobin
HHD	Home hemodialysis

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
HR	Hazard ratio
HS	High school
HSCL	Hopkins Symptom Checklist
HTN	Hypertension
HUI	health utilities index
HUI-3	Health Utilities Index-3
ICD-9	International Classification of Diseases, 9th Revision
IDPN	Intradialytic parenteral nutrition
IDWG	Interdialytic weight gain
IEQ	Illness Effects Questionnaire
IFS-Dialysis	Inventory of Functional Status-Dialysis
IGA	index of general affect
IIEF-5	International Index of Erectile Function, short form
INHD	Incenter nocturnal hemodialysis
IPA	Index of Psychological Affect
IPQ-R	Revised Illness Perception Questionnaire
IQR	Interquartile range
IRR	Incidence rate ratio
IV	Intravenous
IWB	index of well being
KDQ	Kidney Disease Questionnaire
KDQOL SF-36	Kidney Disease Quality of Life Short Form-36
KDQOL	kidney disease quality of life
KDQOL-36	Kidney Disease Quality of Life Short From-36
KDQOL-LF	Kidney Disease Quality of Life-Long Form
KDS2	Kupfer-Detre System-2 questionnaire
Kg	Kilograms
KQ	Key Question
KQ1	Key question 1
KQ2	Key question 2
KQ3	Key question 3
KQ4	Key question 4
K-SADS	Kiddie-Schedule for Affective Disorders and Schizophrenia
Kt/V	Urea clearance
KTIPS	Kidney Transplant Immunosuppressive Protocol Study
L/Rx	Total ultrafiltration in liters per dialysis session
L	Liters
LEVIL	London Evaluation of Illness Survey
LH	Latino/Hispanic
LL	Lower limit
LV	left ventricular
LVESV	Left ventricular end systolic volume
LVM	Left ventricular mass

M^2	Meters squared
MCID	Minimal clinically important difference
MCS	Mental Composite Score
mEq/l	Milliequivalents per liter
MeSH	Medical subject headings
MFI-20	Multidimensional Fatigue Inventory
mg/dl	Milligrams per deciliter
mg/kg	Milligrams per kilogram
mg	Milligrams
Min	Minutes
ml	Milliliter
ml/h/kg	Milliliters per hour per kilogram
ml/hr/kg	Milliliters per hour per kilogram
ml/hr	Milliliters per hour
ml/min	Milliliters per minute
mmHg	Millimeters of mercury
MMSE	Modified Mini-Mental State Examination
MOS	Medical Outcomes Study
MOS-SPI	Medical Outcomes Study Sleep Problem Index
MPP	Medicare as primary payer
MRI	Magnetic Resonance Imaging
MSAS-SF	Memorial Symptom Assessment Scale Short Form
NA	Not available or not applicable
NF-kappaB	Nuclear factor Kappa B
ng/ml	nanograms per milliliter
NHHD	nocturnal home hemodialysis
NKDKTS	National Kidney Dialysis and Kidney Transplantation Study
NNFI	Non-normed fit index
NonESRD	non-end-stage renal disease
NPV	Negative Predictive Value
NR	not reported
NRCT	Nonrandomized controlled trial
NS	Not significant
OR	Odds ratio
PAD	Peripheral arterial disease
PAQOL	Patient Assessed Quality of Life
PAR	Physical Activity Recall questionnaire
PASE	Physical Activity Scale for the Elderly
Patient-yr	Patient-years
PCS	Physical Composite Score
PedsQL	Pediatric Quality of Life Instrument
PedsQL	Pediatric Quality of Life
PF	Physical functioning
PHC	Physical health composite
PHQ	physician’s health questionnaire
PHQ-2	Patient Health Questionnaire-2

PHQ-9	Patient Health Questionnaire-9
PI	Pacific Islander
PICOTS	Populations, Interventions, Comparators, Outcomes, Timing, Setting
POMS	Profile of Mood States
Post grad	Postgraduate degree
PPV	Positive Predictive value
PRAS	Patient Related Anxiety Scale
PROM	Patient reported outcome measure
PROMIS	Patient Reported Outcomes Measurement Information System
PSQI	Pittsburgh Sleep Quality Index
PSQoL	Patient-assessed QOL index
PSS	Pittsburgh Symptom Score Index
PSS-4	PSS-4 Perceived Stress Scale
PTH	Parathyroid hormone
PTSS-10	Post-Traumatic Symptoms Scale-10
PVD	Peripheral vascular disease
PY	Person years or patient-years
QLI	Quality of Life Index
QLI-D	Quality of Life Index-D
QOL	Quality of life
QOLI	Quality of Life Inventory
RAND-36	RAND-36 Measure of Health-Related Quality of Life
RCT	randomized controlled trial
RLS	Restless Leg Severity score
RMSEA	Root mean squared error of approximation
ROBINS-I	Risk of Bias in Nonrandomized Studies-of Interventions
ROBINS-I	Risk of Bias in Nonrandomized Studies-of Interventions
ROC	Receiver Operating Characteristic
RQLP	Renal Quality of Life Profile
RR	Relative risk
RVEDV	Right ventricular end diastolic volume
RVESV	Right ventricular end systolic volume
SBP	Systolic blood pressure
SCID	Structured Clinical Interview for Depression
SD	Standard deviation
SDHD	Short daily hemodialysis
SE	Standard error
SEIQOL-DW	The Schedule of Evaluation of Individual Quality of Life–Direct Weighting
SF-12	Short Form-12
SF-36	Short Form 36
SF-6D	Short Form-6D
SF-MPQ	Short-Form McGill Pain Questionnaire
SIP	Sickness Impact Profile
SOE	Strength of evidence
SPI	Sleep problems index

SPI-II	Medical Outcomes Study Sleep Problems Index-II
SPIRIT	Sharing Patient's Illness Representations to Increase Trust
SPMSQ	Short Portable Mental Status Questionnaire
SPPB	Short Physical Performance Battery
SQLI	Spitzer Quality of Life Index
SWLS	satisfaction with life scale
SWLS	Satisfaction With Life Scale
T3	Triiodothyronine
T4	Thyroxine
TIFL	Time-integrated estimate of extracellular fluid load
TiME	Time to Reduce Mortality in End-Stage Renal Disease Trial
TOO	Task Order Officer
Toronto PreKid	Toronto Pregnancy and Kidney Disease Clinic
TSH	Thyroid-stimulating hormone
U/d	Units per dose
U/kg	Units per kilograms
UL	Upper limit
US	United States
USRDS	U*nited States Renal Data System*
UVol	Urine volume
VAS	Visual Analogue Scale
VETERAN	Veteran End-Stage Renal Disease Study
VO2max	Maximum rate of Oxygen consumption
WBC	White blood cells
White	White, non-Hispanic
WHO	World Health Organization
WNH	White non-Hispanic
Y	Yes
Yr	years

Glossary

End-stage renal disease: Chronic kidney failure with a glomerular filtration rate (GFR) less than 15 mL/min/1.73 m^2 or requiring dialysis.[186]

Quality of life: Multifaceted concept that characterizes a person's positive and negative perspectives on his/her own life, sometimes referred to as well-being. Common domains of quality of life involve physical health, mental health, social relationships, functional status, and work.[187-189]

Validity: "The degree to which a result (of a measurement or study) is likely to be true and free of **bias** (systematic errors). Validity has several other meanings, usually accompanied by a qualifying word or phrase; for example, in the context of measurement, expressions such as 'construct validity', 'content validity' and 'criterion validity' are used."[190]

Construct validity: "Construct validity is the extent to which the measurements used, often questionnaires, actually test the hypothesis or theory they are measuring. Construct validity should demonstrate that scores on a particular test do predict the theoretical trait it says it does. There are two subsets of construct validity: convergent construct validity and discriminant construct validity.[89] In order to have good construct validity one must have a strong relationship with convergent construct validity and no relationship for discriminant construct validity."

Convergent validity: A required component of construct validity, "Convergent construct validity tests the relationship between the construct and a similar measure; this shows that constructs which are meant to be related are related."[89]

Discriminant validity: "Discriminant construct validity tests the relationships between the construct and an unrelated measure; this shows that the constructs are not related to something unexpected." To have good construct validity, there must be no relationship for discriminant construct validity.[89]

Content validity: "Content validity refers to the degree to which an assessment instrument is relevant to, and representative of, the targeted construct it is designed to measure."[191]

Relative validity: "Relative Validity (RV), also referred to as relative precision or relative efficiency, provides an appropriate quantitative index to compare the validity of PRO measures under the conditions in which such measures are typically used. As such, the RV compares two PRO measures on their ability to discriminate patients across disease severity levels and on their ability to detect longitudinal change. Complementary to other psychometric properties such as reliability and respondent burden, the RV is used frequently in literature providing important validity information of PRO measures."[90]

Face validity: "Face validity is a test of internal validity. As the name implies, it asks a very simple question: "On the face of things, do the investigators reach the correct conclusions?"

It requires investigators to step outside of their current research context and assess their observations from a commonsense perspective."[192]

Factorial validity: Factorial validity examines the extent to which the underlying putative structure of a scale is recoverable in a set of test scores…Usually, confirmatory factor analysis or structural equation modeling is used to examine the extent to which the predicted items do indeed form the expected factors.[193]

Concurrent validity: "Concurrent validity is one approach of criterion validity that estimates individual performance on different tests at approximately the same time."[194]

Criterion validity "Criterion validity is a method of test validation that examines the extent to which scores on an inventory or scale correlate with external, non-test criteria." Research in quality of life often tests concurrent validity by measuring score correlations of an established to a new self-reported outcome measure or tool.[195, 196]

Reliability: "The degree to which results obtained by a measurement procedure can be replicated. Lack of reliability can arise from divergences between observers or measurement instruments, measurement error, or instability in the attribute being measured."[190]