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Original Investigation

Timing of Dialysis Initiation, Duration and Frequency of Hemodialysis Sessions, and Membrane Flux: A Systematic Review for a KDOQI Clinical Practice Guideline

Yelena Slinin, MD,[1,2] Nancy Greer, PhD,[1] Areef Ishani, MD,[1,2] Roderick MacDonald, MS,[1] Carin Olson, MD, MS,[2] Indulis Rutks, BS,[1] and Timothy J. Wilt, MD, MPH[1,2]

Background: In 2006, NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) published clinical practice guidelines for hemodialysis adequacy. Recent studies evaluating hemodialysis adequacy as determined by initiation timing, frequency, duration, and membrane type and prompted an update to the guideline.

Study Design: Systematic review and evidence synthesis.

Setting & Population: Patients with advanced chronic kidney disease receiving hemodialysis.

Selection Criteria for Studies: We screened publications from 2000 to March 2014, systematic reviews, and references and consulted the NKF-KDOQI Hemodialysis Adequacy Work Group members. We included randomized or controlled clinical trials in patients undergoing long-term hemodialysis if they reported outcomes of interest.

Interventions: Early versus late dialysis therapy initiation; more frequent (>3 times a week) or longer duration (>4.5 hours) compared to conventional hemodialysis; low- versus high-flux dialyzer membranes.

Outcomes: All-cause and cardiovascular mortality, myocardial infarction, stroke, hospitalizations, quality of life, depression or cognitive function scores, blood pressure, number of antihypertensive medications, left ventricular mass, interdialytic weight gain, and harms or complications related to vascular access or the process of dialysis.

Results: We included 32 articles reporting on 19 trials. Moderate-quality evidence indicated that earlier dialysis therapy initiation (at estimated creatinine clearance [eCl_{cr}] of 10-14 mL/min) did not reduce mortality compared to later initiation (eCl_{cr} of 5-7 mL/min). More than thrice-weekly hemodialysis and extended-length hemodialysis during a short follow-up did not improve clinical outcomes compared to conventional hemodialysis and resulted in a greater number of vascular access procedures (very low-quality evidence). Hemodialysis using high-flux membranes did not reduce all-cause mortality, but reduced cardiovascular mortality compared to hemodialysis using low-flux membranes (moderate-quality evidence).

Limitations: Few studies were adequately powered to evaluate mortality. Heterogeneity of study designs and interventions precluded pooling data for most outcomes.

Conclusions: Limited data indicate that earlier dialysis therapy initiation and more frequent and longer hemodialysis did not improve clinical outcomes compared to conventional hemodialysis.

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INDEX WORDS: Hemodialysis (HD); hemodialysis adequacy; dialysis initiation; dialysis frequency; hemodialysis session duration; blood pressure; volume control; dialysis membrane flux; chronic kidney disease (CKD); systematic review; clinical practice guideline; National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI); clinical outcomes; end-stage renal disease (ESRD).

Nearly 400,000 patients are treated with hemodialysis in the United States. Medicare spending approaches $90,000 per patient per year of care.[1] Despite increasing care costs, patients receiving hemodialysis experience suboptimal outcomes, with mortality rates up to 8 times that of the age-matched general population.[1] The NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) clinical practice guidelines and recommendations for hemodialysis adequacy were introduced in 2006.[2] Since publication of these guidelines, evidence has evolved. The NKF convened a work group to update portions of their guideline potentially affected by new evidence.

To inform the work of the NKF-KDOQI Hemodialysis Adequacy Work Group (whose clinical practice guidelines update appears elsewhere in this issue of *AJKD*[3]), we conducted a systematic review to determine whether clinical and patient-centered outcomes in patients with advanced chronic kidney disease (CKD) were improved by the following: (1) earlier

From the [1]Minneapolis Veterans Affairs Healthcare System; and [2]Department of Medicine, University of Minnesota, Minneapolis, MN.

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Address correspondence to Yelena Slinin, MD, Minneapolis Veterans Affairs Healthcare System, 1 Veterans Dr (J111), Minneapolis, MN 55417. E-mail: yelena.slinin@va.gov

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hemodialysis therapy initiation, (2) more frequent or longer duration hemodialysis compared to conventional hemodialysis, or (3) use of low-flux compared with high-flux membranes. Key questions were formulated by the evidence review team together with the guideline work group. This article focuses on the following key questions in the guideline update. (1) In patients with advanced CKD, does initiating dialysis therapy earlier (as defined by higher glomerular filtration rate [GFR] at dialysis therapy initiation) improve outcomes? (2) In hemodialysis patients, does more frequent hemodialysis (>3 times a week) improve outcomes compared to less frequent hemodialysis? (3) In hemodialysis patients, does extended hemodialysis duration (>4.5-hour sessions) improve outcomes compared to usual-length hemodialysis duration? (4) Do patients with extended (longer) or more frequent hemodialysis have greater blood pressure and volume control compared with patients with shorter or less frequent dialysis? (5) In hemodialysis patients, do high-flux membranes improve patient outcomes when compared to low-flux hemodialysis? We also addressed harms relevant to each question.

METHODS

Overview

In consultation with the NKF-KDOQI Hemodialysis Adequacy Clinical Practice Guidelines Update Work Group, we developed and followed a standard protocol for all steps of the review process. A full technical report (Item S1, available as online supplementary material) provides the analytic framework, detailed literature search strategies, and results for the original key questions.

Search Strategy

We developed a search strategy including terms for hemodialysis, CKD, and specific topics of interest for this review: initiation of hemodialysis therapy, hemodialysis frequency, duration of hemodialysis sessions, interdialytic weight gain, ultrafiltration rate, blood pressure and volume control, and membrane flux (Item S2). We included search strings to identify randomized controlled trials (RCTs), controlled clinical trials (CCTs), and systematic reviews or meta-analyses. We searched MEDLINE (Ovid) from 2000 to March 2014 for English-language studies in populations of all ages. We searched reference lists of recent systematic reviews and studies eligible for inclusion to identify studies not identified in our MEDLINE search. We searched ClinicalTrials.gov to identify recently completed studies and obtained input from members of the work group.

Study Selection

Abstracts identified by the literature search were triaged by an investigator or trained research associate (YS, NG, AI, RM). We retrieved for full-text review any RCT, CCT, systematic review, or meta-analysis of hemodialysis for CKD related to the topics of interest. Two investigators or research associates (YS, NG, AI) reviewed the full text of articles identified from the abstract review or from other reference lists. Articles were potentially eligible if they involved long-term hemodialysis for CKD and provided outcomes of interest: all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, all-cause hospitalization, quality of life, depression or cognitive function scores, systolic blood pressure, number of antihypertensive medications, left ventricular mass, interdialytic weight gain, dry weight, or harms or complications related to vascular access (eg, access failure) or the process of dialysis (eg, hospitalization due to fluid disorders). We excluded crossover trials with hemodialysis session duration less than 28 days in each treatment arm.

For timing of dialysis therapy initiation (key question 1), we included RCTs in humans with advanced CKD that assigned individuals to different timing of dialysis therapy initiation (as defined by estimated kidney function at initiation) and reported outcomes of interest.

For frequency and duration of hemodialysis sessions (key questions 2-4), we included RCTs or CCTs in humans receiving long-term hemodialysis that assigned individuals to more frequent hemodialysis (>3 times a week) or longer duration (>4.5 hours) dialysis versus conventional hemodialysis and reported outcomes of interest.

For studies that compared low-flux with high-flux dialysis membranes (key question 5), we included RCTs or CCTs that enrolled at least 50 participants with chronic kidney failure in each treatment arm, with a minimum of 12 months' follow-up.

Data Extraction and Risk of Bias Assessment

We extracted study and intervention characteristics; follow-up period and withdrawals; inclusion/exclusion criteria; patient characteristics; primary, secondary, and intermediate outcomes; and harms. Extraction was done by one research associate or investigator (NG, CO, RM) and verified by a second (RM, CO, NG).

We assessed risk of bias of individual studies based on methods used by the Cochrane Collaboration. Studies were rated as low, moderate, or high risk of bias based on the following: sequence generation, allocation concealment, blinding, completeness of outcome data and use of intention-to-treat analysis, and selective outcome reporting and description of withdrawals.[4] CCTs were rated at least moderate risk of bias because allocation was not randomized.

Data Synthesis, Analysis, and Overall Quality Rating

Results were pooled if clinical heterogeneity of patient populations, interventions, and outcomes was minimal. Data were analyzed in Review Manager, version 5.2.[5] Random-effects models were used to generate risk ratios (RRs) and 95% confidence intervals (CIs) for mortality outcomes. When available, hazard ratios (HRs) as reported in trials are presented in table footnotes. Statistical heterogeneity was summarized using the I^2 statistic (50% indicates moderate heterogeneity, and ≥75% indicates substantial heterogeneity).[6] Due to heterogeneity of study designs and interventions, we did not pool data for most outcomes. Other outcomes were summarized narratively. Quality of the overall body of evidence for a specific outcome was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Item S3).[7] We added an additional level, "insufficient," indicating evidence was unavailable.

RESULTS

Included Studies

Our literature search for the full review yielded 3,701 abstracts (Fig 1). During abstract triage, we excluded 3,420 abstracts and identified 281 articles for full-text review. Because we performed individual searches for the different topic areas, there were 92 duplicate citations. Hand searching of systematic