KDOQI CLINICAL PRACTICE GUIDELINE FOR HEMODIALYSIS ADEQUACY: 2015 UPDATE

Abstract

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) has provided evidence-based guidelines for all stages of chronic kidney disease (CKD) and related complications since 1997. The 2015 update of the KDOQI Clinical Practice Guideline for Hemodialysis Adequacy is intended to assist practitioners caring for patients in preparation for and during hemodialysis. The literature reviewed for this update includes clinical trials and observational studies published between 2000 and March 2014. New topics include high-frequency hemodialysis and risks; prescription flexibility in initiation timing, frequency, duration, and ultrafiltration rate; and more emphasis on volume and blood pressure control. Appraisal of the quality of the evidence and the strength of recommendations followed the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach. Limitations of the evidence are discussed and specific suggestions are provided for future research.

Keywords: Hemodialysis; Clinical Practice Guideline; hemodialysis prescription; hemodialysis frequency; initiation; adequacy; treatment time; hemofiltration; urea modeling; evidence-based recommendation; KDOQI.

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NOTICE

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon the best information available as of June 2015. It is designed to provide information and assist decision making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

Kidney Disease Outcomes Quality Initiative (KDOQI) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is on file at the National Kidney Foundation (NKF).

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Abbreviations and Acronyms

ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
AV	Arteriovenous
avCpre	Average predialysis blood urea nitrogen
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CANUSA	Canadian-USA Study on Adequacy of Peritoneal Dialysis
CI	Confidence interval
Ci	Dialysate inlet conductivities
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL_{cr}	Creatinine clearance
Co	Dialysate outlet conductivities
CV	Cardiovascular
D	Dialysance
DRIP	Dry Weight Reduction Intervention
ECV	Extracellular volume
eGFR	Estimated glomerular filtration rate
eKt/V	Equilibrated Kt/V
ERT	Evidence Review Team
ESA	Erythropoiesis-stimulating agent
ESHOL	Estudio de Supervivencia de Hemodiafiltración On-Line
ESRD	End-stage renal disease
FHN	Frequent Hemodialysis Network
G	Urea generation
GFAC	G-factor
GFR	Glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HD	Hemodialysis
HEMO	NIH study of HD dose and membrane flux
HR	Hazard ratio
IDEAL	Initiating Dialysis Early and Late
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
Kru	Residual kidney function
KRT	Kidney replacement therapy
LVH	Left ventricular hypertrophy
MDRD	Modification of Diet in Renal Disease
mGFR	Measured glomerular filtration rate
MPO	Membrane Permeability Outcome
Na	Sodium
NCDS	National Cooperative Dialysis Study
NECOSAD	Netherlands Cooperative Study on the Adequacy of Dialysis
NIH	National Institutes of Health
NKF	National Kidney Foundation
NS	Not specified
PCR	Protein catabolic rate
PD	Peritoneal dialysis
PIDI	Preceding interdialysis interval
Pru	Percent reduction in urea concentration
Qb	Blood flow rate
Qd	Dialysate flow rate
Qf	Ultrafiltration flow
R	Ratio of postdialysis to predialysis BUN
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial
RR	Relative risk
SA-sdtKt/V	Surface area–adjusted standard Kt/V
Scr	Serum creatinine
Scys	Serum cystatin C
sp	Single-pool (Kt/V)
std	Standard (Kt/V)
T	Treatment time in hours
TiME	Time to Reduce Mortality in End-Stage Renal Disease trial
Uf	Ultrafiltration rate
URR	Urea reduction ratio
USRDS	US Renal Data System
V	Urea volume

Current CKD Nomenclature Used by KDOQI

CKD Categories	Definition
CKD	CKD of any stage (1-5), with or without a kidney transplant, including both non–dialysis-dependent CKD (CKD 1-5ND) and dialysis-dependent CKD (CKD 5D)
CKD ND	Non–dialysis-dependent CKD of any stage (1-5), with or without a kidney transplant (ie, CKD excluding CKD 5D)
CKD T	Non–dialysis-dependent CKD of any stage (1-5) with a kidney transplant
Specific CKD Stages	
CKD 1, 2, 3, 4	Specific stages of CKD, CKD ND, or CKD T
CKD 3-4, etc	Range of specific stages (eg, both CKD 3 and CKD 4)
CKD 5D	Dialysis-dependent CKD 5
CKD 5HD	Hemodialysis-dependent CKD 5
CKD 5PD	Peritoneal dialysis–dependent CKD 5

Executive Summary

When hemodialysis (HD) was introduced as an effective workable treatment in 1943,[1] the outlook for patients with advancing kidney failure suddenly changed from anticipation of impending death to indefinite survival. Since then, implementation of dialysis has advanced from an intensive bedside therapy to a more streamlined treatment, sometimes self-administered in the patient's home, using modern technology that has simplified dialysis treatment by reducing the time and effort required by the patient and caregivers. Standards have been established to efficiently care for large numbers of patients with a balance of resources and patient time. However, simplified standards can lead to inadequate treatment, so guidelines have been developed to assure patients, caregivers, and financial providers that reversal of the uremic state is the best that can be offered and complications are minimized. The National Kidney Foundation (NKF) continues to sponsor this forum for collaborative decision making regarding the aspects of HD that are considered vital to achieve these goals.

Over 400,000 patients are currently treated with HD in the United States, with Medicare spending approaching $90,000 per patient per year of care in 2012.[2] Unfortunately, although mortality rates are improving (30% decline since 1999), they remain several-fold higher than those of age-matched individuals in the general population, and patients experience an average of nearly 2 hospital admissions per year.[3] Interventions that can improve outcomes in dialysis are urgently needed. Attempts to improve outcomes have included initiating dialysis at higher glomerular filtration rates (GFRs), increasing dialysis frequency and/or duration, using newer membranes, and employing supplemental or alternative hemofiltration. Efforts to increase the dose of dialysis administered 3 times weekly have not improved survival, indicating that something else needs to be addressed.

GATHERING THE EVIDENCE

The literature reviewed for this adequacy update includes observational studies and clinical trials published from 2000 to 2014. In some cases, high-quality data have been presented to support conclusions, but in most cases, clinicians are left with incomplete or inadequate data. In these situations, as in many aspects of general medical care, decisions about treatments must be based on logic and observation. A major goal of the Work Group and Evidence Review Team (ERT) was to compile and evaluate as much information as possible to arrive at a reasonable answer to the questions posed in Box 1,

not all of which can be answered definitively with support from controlled clinical trials.

Initiating HD

Despite lack of evidence from randomized controlled trials (RCTs) about the optimal time to start kidney replacement therapy (KRT), there has been a trend, which has leveled off since 2010, in the United States toward earlier initiation of dialysis at higher levels of kidney function.[2,3] If earlier dialysis is ineffective, this trend would lead to greater resource utilization without clinical benefit. Published in 2010, results of the IDEAL (Initiating Dialysis Early and Late) trial explored this issue, and data from this trial constitute the best evidence regarding timing of dialysis initiation, motivating the update of this guideline.[4]

Frequency and Duration of Dialysis

Observational and controlled nonrandomized studies had suggested that more frequent and/or longer dialysis improves the patient's quality of life, controls hyperphosphatemia, reduces hypertension, and results in regression of left ventricular hypertrophy (LVH).[5,6]

Box 1. Questions Posed at the Start of the Update Initiative

> In patients with CKD, does starting dialysis earlier improve outcomes?
>
> What harms result from starting dialysis earlier?
>
> In patients with end-stage kidney disease, does more frequent hemodialysis (>3 times a week) improve outcomes compared to less frequent hemodialysis?
>
> What harms result from more frequent hemodialysis?
>
> In patients with end-stage kidney disease, does extended-duration hemodialysis improve outcomes compared to usual-length hemodialysis?
>
> What harms result from extended hemodialysis?
>
> Do patients with high interdialytic weight gains and high ultrafiltration rates have worse outcomes compared with patients with lower interdialytic weight gains and low ultrafiltration rates?
>
> 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?
>
> Is improvement of blood pressure and volume control associated with improved clinical outcomes according to length or frequency of dialysis sessions?
>
> In patients with stage 5 CKD, do high-flux membranes improve patient outcomes when compared to hemodialysis with low-flux membranes?
>
> In patients with stage 5 CKD, does hemodiafiltration improve patient outcomes when compared to high-flux hemodialysis?
>
> What harms result from use of high-flux membranes compared to low-flux membranes or from use of hemodiafiltration?

Abbreviation: CKD, chronic kidney disease.

Based on these findings, more frequent and longer dialysis sessions have become more common. Since the previous KDOQI (Kidney Disease Outcomes Quality Initiative) update,[7] several RCTs that compared more frequent or extended dialysis to conventional dialysis have been completed.[8-11] This update reviews this evidence.

Membranes and Hemodiafiltration Versus HD

Cardiovascular (CV) disease is the leading cause of death in patients with CKD stage 5,[2] with uremic toxins and the kidney failure milieu including volume expansion likely important contributing factors. Compared to low-flux dialysis, high-flux dialysis and convective therapies such as hemofiltration and hemodiafiltration provide higher clearance of larger solutes, removal of which might improve CV outcomes. This update reviews the evidence for use of high-flux compared to low-flux dialyzer membranes, as well as convective modes of KRT compared to conventional HD.

Small-Solute Clearance

This update addresses only the dialysis treatment while acknowledging that there are limits to what dialysis can accomplish. Assessment of dialysis requires measurement of the dialysis dose. Included herein are the current recommended methods for measuring what dialysis does best, the purging of small dialyzable solutes, with the assumption that this function is the essence of the life-prolonging effect of dialysis. However, while optimization of small-solute removal should be considered the first priority, assessment of dialysis adequacy should not stop there as the absence of native kidneys entails loss of many vital functions, only one of which is small-solute removal.

Adverse Effects of Dialysis

Early investigators postulated that exposure of the blood to a large foreign surface for several hours would cause an inflammatory response in the patient and deplete vital constituents of the blood, such as platelets and clotting factors. Removal of low-molecular-weight hormones, vitamins, and other vital molecules was also a concern. Membranes were developed to be "biocompatible," causing less interaction with blood constituents. While the postulated depletion syndromes apparently never materialized, in recent years, concern has been raised about transient intra- and postdialysis alkalosis and dialysis-associated reductions in blood pressure (BP), serum potassium, and serum phosphorus and changes in other electrolytes and proteins that may amount to a "perfect storm" of stress potentially responsible for acute cardiac events, as well as long-term effects on the brain and CV system.[12-14] More frequent and more prolonged dialysis, while improving solute clearance and volume removal, could enhance blood-membrane interaction, add to the burden on patients and caregivers,[15] and even accelerate loss of native kidney function and vascular access damage.[16,17] The current guideline update includes a listing and recommendations regarding potential benefits and adverse effects associated with more frequent dialysis.

Limitations of "Adequacy"

The ultimate goal of treatment for patients with CKD stage 5 is improvement in quality of life, with prolongation of life often an additional goal. This requires more than the dialysis treatment itself. In recent literature, adequacy of dialysis is sometimes confused with adequacy of other aspects of patient management, with the erroneous assumption that having achieved dialysis adequacy, the goal of dialysis has been accomplished. In the opinion of the Work Group, this is incorrect: it is important to distinguish adequacy of the dialysis from adequacy of patient care. Dialysis-dependent patients require a number of treatments independent of or only partially dependent on the dialysis itself, many of which were implemented long before the patient's dialysis started. Guidelines for some of these are addressed in other publications by KDOQI, including management of anemia, nutrition, metabolic bone disease, diabetes, and CV disease.[18-22]

STRUCTURE OF THE WORK GROUP

The volunteer members of the Work Group were selected for their clinical experience, as well as experience with clinical trials and familiarity with the literature, especially regarding the issues surrounding dialysis adequacy. All are practicing nephrologists who have many years of experience with care of patients dependent on KRT.

METHODS

In consultation with the KDOQI Hemodialysis Adequacy Clinical Practice Guidelines Update Work Group, the Minnesota ERT developed and followed a standard protocol for all steps of the review process. The guideline update effort was a multidisciplinary undertaking that included input from NKF scientific staff, the ERT from the Center for Chronic Disease Outcomes Research at the Minneapolis Veterans Affairs Medical Center, and the Work Group. The comprehensive findings from the systematic literature review prepared for this update are presented in detail in the accompanying article from Slinin et al.[23] Briefly, MEDLINE (Ovid) was searched from 2000 to March 2014 for English-language studies in populations of all ages. Additional searches included reference lists of recent systematic reviews and studies eligible for inclusion to identify relevant studies not identified in

Box 2. Summary of Recommendation Statements

Guideline 1: Timing of Hemodialysis Initiation

1.1 Patients who reach CKD stage 4 (GFR < 30 mL/min/1.73 m^2), including those who have imminent need for maintenance dialysis at the time of initial assessment, should receive education about kidney failure and options for its treatment, including kidney transplantation, PD, HD in the home or in-center, and conservative treatment. Patients' family members and caregivers also should be educated about treatment choices for kidney failure. (*Not Graded*)

1.2 The decision to initiate maintenance dialysis in patients who choose to do so should be based primarily upon an assessment of signs and/or symptoms associated with uremia, evidence of protein-energy wasting, and the ability to safely manage metabolic abnormalities and/or volume overload with medical therapy rather than on a specific level of kidney function in the absence of such signs and symptoms. (*Not Graded*)

Guideline 2: Frequent and Long Duration Hemodialysis

In-center Frequent HD

2.1 We suggest that patients with end-stage kidney disease be offered in-center short frequent hemodialysis as an alternative to conventional in-center thrice weekly hemodialysis after considering individual patient preferences, the potential quality of life and physiological benefits, and the risks of these therapies. (*2C*)

2.2 We recommend that patients considering in-center short frequent hemodialysis be informed about the risks of this therapy, including a possible increase in vascular access procedures (*1B*) and the potential for hypotension during dialysis. (*1C*)

Home Long HD

2.3 Consider home long hemodialysis (6-8 hours, 3 to 6 nights per week) for patients with end-stage kidney disease who prefer this therapy for lifestyle considerations. (*Not Graded*)

2.4 We recommend that patients considering home long frequent hemodialysis be informed about the risks of this therapy, including possible increase in vascular access complications, potential for increased caregiver burden, and accelerated decline in residual kidney function. (*1C*)

Pregnancy

2.5 During pregnancy, women with end-stage kidney disease should receive long frequent hemodialysis either in-center or at home, depending on convenience. (*Not Graded*)

Guideline 3: Measurement of Dialysis: Urea Kinetics

3.1 We recommend a target single pool Kt/V (spKt/V) of 1.4 per hemodialysis session for patients treated thrice weekly, with a minimum delivered spKt/V of 1.2. (*1B*)

3.2 In patients with significant residual native kidney function (Kru), the dose of hemodialysis may be reduced provided Kru is measured periodically to avoid inadequate dialysis. (*Not Graded*)

3.3 For hemodialysis schedules other than thrice weekly, we suggest a target standard Kt/V of 2.3 volumes per week with a minimum delivered dose of 2.1 using a method of calculation that includes the contributions of ultrafiltration and residual kidney function. (*Not Graded*)

Guideline 4: Volume and Blood Pressure Control: Treatment Time and Ultrafiltration Rate

4.1 We recommend that patients with low residual kidney function (< 2 mL/min) undergoing thrice weekly hemodialysis be prescribed a bare minimum of 3 hours per session. (*1D*)

    4.1.1 Consider additional hemodialysis sessions or longer hemodialysis treatment times for patients with large weight gains, high ultrafiltration rates, poorly controlled blood pressure, difficulty achieving dry weight, or poor metabolic control (such as hyperphosphatemia, metabolic acidosis, and/or hyperkalemia). (*Not Graded*)

4.2 We recommend both reducing dietary sodium intake as well as adequate sodium/water removal with hemodialysis to manage hypertension, hypervolemia, and left ventricular hypertrophy. (*1B*)

    4.2.1 Prescribe an ultrafiltration rate for each hemodialysis session that allows for an optimal balance among achieving euvolemia, adequate blood pressure control and solute clearance, while minimizing hemodynamic instability and intradialytic symptoms. (*Not Graded*)

Guideline 5: New Hemodialysis Membranes

5.1 We recommend the use of biocompatible, either high or low flux hemodialysis membranes for intermittent hemodialysis. (*1B*)

MEDLINE and ClinicalTrials.gov to identify any recently completed studies.

ERT Study Selection and Outcomes of Interest

Studies were included if they were randomized or controlled clinical trials in people treated with, initiating, or planning to initiate maintenance HD for CKD. To be included, studies needed to report the effects of an intervention on all-cause mortality, CV mortality, myocardial infarction, stroke, all-cause hospitalization, quality of life, depression or cognitive performance, BP or BP treatment, left ventricular mass, interdialytic weight gain, dry weight, or harms or complications related to vascular access or the process of dialysis. Observational studies considered by the Work Group that were not selected by the evidence

Table 1. Grade for Strength of Recommendation

Grade[a]	Implications		
	Patients	**Clinicians**	**Policy**
Level 1 (strong recommendation): "We Recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be adopted as policy in most situations.
Level 2 (conditional recommendation/ suggestion): "We Suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Based on Uhlig et al.[24]

[a]The additional category "Not Graded" was used, typically to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

team and are not included in the Evidence Report by the ERT include those evaluating mortality, hard outcomes, and pregnancy-related outcomes with frequent dialysis.

For frequency and duration of HD sessions, trials that assigned individuals to more frequent HD (>3 times a week) or longer (>4.5 hours) dialysis versus conventional HD were included. For studies that compared high-flux to low-flux dialysis membranes or hemofiltration or hemodiafiltration to conventional HD, the ERT included trials that enrolled at least 50 participants with a minimum of 12 months' follow-up in each treatment arm.

GUIDELINE STATEMENTS

The Work Group distilled these answers in the form of 5 guidelines, some of which are similar to the previous guidelines published in 2006[7] but have been re-emphasized or reinterpreted in light of new data (Box 2). For each of the guidelines, the quality of the evidence and the strength of the recommendations were graded separately using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach criteria[24]: scales of A to D for quality of the evidence and 1 or 2 for strength of the recommendation, including its potential clinical impact (Table 1; Box 3). The guideline statements were based on a consensus within the Work Group that the strength

of the evidence was sufficient to make definitive statements about appropriate clinical practice. When the strength of the evidence was not sufficient to make such statements, the Work Group offered recommendations based on the best available evidence and expert opinion. In cases in which controversy exists but data are sparse, the guideline is ungraded, based on consensus opinion of the Work Group. For a few of the guidelines, not all of the Work Group members agreed, and in such cases, the reasons for disagreement are spelled out in the rationale that follows the guideline statement. For all guidelines, clinicians should be aware that circumstances may appear that would require straying from the recommendations of the Work Group.

Box 3. Grade for Quality of Evidence

A: High quality of evidence. We are confident that the true effect lies close to that of the estimate of the effect.

B: Moderate quality of evidence. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

C: Low quality of evidence. The true effect may be substantially different from the estimate of the effect.

D: Very low quality of evidence. The estimate of effect is very uncertain and often will be far from the truth.

Guideline 1: Timing of Hemodialysis Initiation

1.1 **Patients who reach CKD stage 4 (GFR < 30 mL/min/1.73 m^2), including those who have imminent need for maintenance dialysis at the time of initial assessment, should receive education about kidney failure and options for its treatment, including kidney transplantation, PD, HD in the home or in-center, and conservative treatment. Patients' family members and caregivers also should be educated about treatment choices for kidney failure. (*Not Graded*)**

1.2 **The decision to initiate maintenance dialysis in patients who choose to do so should be based primarily upon an assessment of signs and/or symptoms associated with uremia, evidence of protein-energy wasting, and the ability to safely manage metabolic abnormalities and/or volume overload with medical therapy rather than on a specific level of kidney function in the absence of such signs and symptoms. (*Not Graded*)**

RATIONALE FOR GUIDELINE 1.1

Recent KDIGO (Kidney Disease: Improving Global Outcomes) and prior KDOQI guidelines recommend referral of all individuals with GFR < 30 mL/min/1.73 m^2 to a nephrologist, stressing that timely nephrology referral maximizes the likelihood of adequate planning for KRT to optimize decision making and outcomes.[7,25,26] While determining the rate of progression and precise timing of referral is beyond the scope of this guideline, the implication is clear—that patients, their families, and caregivers should have ample time to make informed decisions regarding KRT and to implement these decisions successfully.[27]

Multiple dialysis modalities are available for KRT, including modalities performed in the home and modalities in dialysis facilities, none of which is conclusively demonstrated to be superior to the others.[28,29] Additionally, conservative nondialysis care may be the appropriate decision for many older or more infirm individuals,[30] while pre-emptive or early transplantation may be the best for many other patients. In patients considering maintenance dialysis, it is important to acknowledge that each KRT modality adds a unique burden of treatment to the already high burden of disease. In this context, patients, their families, and their caregivers are best positioned to determine which tradeoffs they are willing to make, particularly given the lack of definitive evidence for the superiority of one

dialysis modality over the other and the possibility that conservative care may be the option that best fits some individual patients' goals. Morton and colleagues[31] recently provided a thematic synthesis of 18 qualitative studies that reported the experience of 375 patients and 87 caregivers. They identified 4 major themes central to treatment choices: confronting mortality (choosing life or death, being a burden, living in limbo), lack of choice (medical decision, lack of information, constraints on resources), gaining knowledge about options (peer influence, timing of information), and weighing alternatives (maintaining lifestyle, family influence, maintaining status quo). However, none of the essential decisions can be made in an informed manner without adequate time for education and contemplation.

As illustrated by Morton and colleagues' systematic review, electing conservative therapy rather than dialysis or kidney transplantation is an important option for many people with kidney failure. In one study of 584 patients with CKD stages 4 and 5, a total of 61% of the patients who had started HD regretted this decision,[30] and when asked why they chose dialysis, 52% attributed this decision to their physician. While this study is limited by a homogeneous population, it is apparent that education prior to dialysis regarding treatment options was insufficient in many, and that this led to dissatisfaction with KRT decisions. The limited ability of care providers to predict patient choice was illustrated by a recent study reporting on focus groups and interviews with 11 nephrologists and 29 patients older than 65 years with advanced CKD.[32] Both patients and nephrologists acknowledged that discussions about prognosis are rare and patients cope most often with their diagnosis through avoidance, while nephrologists expressed concern over evoking negative reactions if they challenge this coping strategy. The Work Group recognizes that the experiences reported in this study are not unique to these patients and physicians; accordingly, we stress the need for patient-centered education to begin early; to involve patients, their families, and their caregivers, if possible; and to be continually reinforced in a positive and patient-sensitive manner.[27,31] Further, given the high prevalence of cognitive impairment[33] and delirium[34] among patients with kidney failure, as well as acknowledged difficulties predicting the rate of progression to kidney failure among patients with advanced CKD,[35-38] it is imperative that patients' informants and proxy decision makers be involved in this decision-making process.

Few clinical trials have evaluated the potential benefits of referral and education prior to the need for dialysis[39,40]; accordingly, statements made on this

topic are based on opinion and observational reports. In one US setting where predialysis education was evaluated, individuals participating in an educational program were more than 5 times more likely than patients who did not receive such education to initiate peritoneal dialysis (PD) and twice as likely to initiate HD with an arteriovenous (AV) fistula or a graft. Notably, in this observational study, the mortality rate among those participating in the educational program was half that seen in controls.[41] However, even with timely education, many CKD patients may not initiate dialysis with their chosen modality; the reasons for this remain uncertain.[42]

Studies over the last 2 decades indicate that most patients starting maintenance dialysis in the United States are unaware of options for KRT other than in-center HD.[43,44] Despite the introduction of a Medicare benefit for CKD education over 5 years ago,[45] many nephrology practices have not implemented structured education programs for stage 4 CKD patients and their families[46]; it is the hope of this Work Group that this gap in availability of patient education will be eventually bridged. Acknowledging that the course of many dialysis initiations may be suboptimal, quality improvement initiatives suggest that intensive education should continue even following the initiation of dialysis.[47,48]

Guideline 1.1 specifically includes those who have an imminent need for KRT. Whenever possible, the timing of presentation should not limit the treatment options for kidney failure. Although logistically, HD is easiest to implement, PD and conservative care are important options.[27,49-51] In the recent Choosing Wisely campaign, the American Society of Nephrology proposed that dialysis should not be initiated without ensuring a shared decision-making process among patients, their families and caregivers, and their physicians.[52] In the opinion of the Work Group, this statement is appropriate for both planned and urgent dialysis initiations.

The Work Group acknowledges that there is tremendous heterogeneity in kidney disease progression. There are people with CKD stage 3 who may be rapid progressors who will benefit from earlier multidisciplinary education, while there also are many people with CKD stage 4 who ultimately will not receive dialysis. Accordingly, we acknowledge that there is no perfect threshold for all patients at which multidisciplinary education and preparation for kidney failure should be initiated. For those who do not end up progressing to kidney failure, education and preparation for dialysis may result in costs and stresses that may not have otherwise been incurred; however, in generating this recommendation, the Work Group believed strongly that patient empowerment, which is enabled by providing timely knowledge both of prognosis and of treatment options followed by sufficient time and ability to assess these options, outweighed these potential disadvantages. In this context, the Work Group noted that the purpose of dialysis is not solely prolongation of life but rather promotion of living. Accordingly, it is essential that dialysis initiation or the decision to forgo KRT be an individualized process and that this process incorporates eliciting patient goals and life preferences, prognosis, and expected benefits and burdens associated with kidney failure and its treatment, followed by guidance and decision support regarding the therapies that can offer the patient the greatest likelihood of achieving their goals within their preference structure.

Research Recommendations

Although improvements have been made in this area, as demonstrated by Tangri and colleagues,[53] better predictive instruments for determining when, if ever, an individual is likely to require KRT are important for optimizing patient preparation, including timely creation of vascular access, PD catheter placement, and pre-emptive transplantation, while minimizing unnecessary procedures such as vascular access surgeries and donor and recipient transplantation evaluations. Additionally, research regarding how to conduct patient education and to facilitate the decision-making process when challenged with the need for KRT has the potential to enhance individualized patient care.

RATIONALE FOR GUIDELINE 1.2

The balance among the benefits, risks, and disadvantages of initiating or not initiating dialysis should be evaluated, taking into account education received and preferences expressed by the patients and/or their caregivers. Symptoms of uremia are nonspecific, and attempts should be made to evaluate for other, sometimes reversible, causes of symptoms. Moreover, uremic symptoms can be subtle, and patients may adapt to lower levels of functioning or well-being without clearly expressing symptoms. The decision to initiate KRT should not be based on estimated GFR (eGFR) level alone, in large part reflecting the imprecision of measurement, regardless of the method of assessment of kidney function. Although not included in the guideline statement, the Work Group noted that there likely is a floor GFR below which KRT is required, conveying the point that despite the lack of data regarding a specific GFR threshold and difficulties inherent in precisely determining GFR, there is a level at which electing for KRT initiation versus electing for conservative care becomes imperative.

While there is a need to estimate kidney function in patients with CKD and the level of kidney function should be considered when determining the timing of dialysis initiation, the Work Group thought that sufficient data exist to discourage reliance on a specific eGFR level. In patients with advanced CKD, serum creatinine–based estimating equations are substantially influenced by muscle mass, making eGFR both a marker of sarcopenia and kidney function. Consistent with this, while most cohort studies assessing the association between eGFR at initiation of dialysis and mortality have shown a higher risk for death with higher eGFR (Table 2), the same association is not demonstrable with measured clearances (Table 3).[54]

Currently, serum creatinine–based estimating equations are the most commonly used method to estimate GFR (Table 4); however, serum creatinine has limitations as a filtration marker because generation of creatinine may vary, most notably reflecting different levels of muscle mass, as noted above (Box 3).[55] Most commonly, in patients with advanced kidney disease, low muscle mass may result in overestimation of GFR (Table 5). To assist the decision-making process and better align clinical symptoms with GFR, in selected cases, direct measurement of GFR, measurement of filtration markers in the urine, and measures of serum cystatin C and other serum biomarkers of kidney function that are not dependent on muscle mass may yield more precise estimates in people with advanced kidney disease.[55,56] Ongoing investigations of existing and novel biomarkers ultimately may lead to improved estimates of GFR that can optimize the timing of dialysis initiation.

Accordingly, although favoring eGFR rather than serum creatinine as an indicator of kidney function, the Work Group elected not to recommend a specific GFR estimating equation for use in advanced CKD as this is a rapidly evolving field with increasing use of novel biomarkers that may improve predictions. Additionally, the Work Group favored not recommending routine 24-hour urine collections of filtration markers, but recognizes the potential utility of this in clinical situations in which symptoms of uremia appear discordant with the level of kidney function.

Despite the larger body of evidence that has accumulated since the prior KDOQI guideline, the recommendation for timing of dialysis initiation in this update does not markedly differ from the prior KDOQI guideline. The most important study that informs this guideline is the IDEAL Study.[4] In this clinical trial conducted in 32 centers in Australia and New Zealand, 828 adult patients with creatinine clearance of 10 to 15 mL/min/1.73 m^2 were randomized to begin dialysis treatment earlier (10-14 mL/min/1.73 m^2; n = 404) or later (5-7 mL/min/1.73 m^2; n = 424). Upon follow-up, 19% of participants assigned to start dialysis early started later, and 76% of participants assigned to start dialysis late started early. Hence, mean creatinine clearance at the time of initiation of dialysis in the early and late groups was 12.0 and 9.8 mL/min (eGFR, 9.0 vs 7.8 mL/min/1.73 m^2), and the median difference in time to dialysis initiation was 5.6 months. There was no significant difference in time to death, CV or infectious events, or complications of dialysis.[57] These results did not differ even when the analyses were restricted to individuals who started treatment with PD. Furthermore, the trend for higher total health care costs in individuals assigned to start dialysis early was not significantly different,[58] and in a substudy, there was no difference in cardiac structure or function between earlier and later start groups.[59]

One limitation of the IDEAL Study was that the targeted degree of separation in creatinine clearance at the time of dialysis initiation was not achieved; this most often was due to earlier-than-planned initiation of dialysis due to symptoms of uremia in individuals randomized to a late start. Of note, IDEAL contrasts with many observational studies as there was no signal of harm with initiation of dialysis at higher levels of kidney function in IDEAL. By design, IDEAL participants were healthier than seen in routine clinical practice; most IDEAL participants had extensive pre-existing nephrology care and only 6% of IDEAL participants had a history of congestive heart failure as compared to one-third of the incident dialysis population in the United States.[60] Despite these limitations, the Work Group recognizes that IDEAL was an exceedingly difficult trial to conduct and notes that it is unlikely that another clinical trial of dialysis initiation will be undertaken in the near future.

The results of the IDEAL Study and observational studies allowed the Work Group to make a few key conclusions. First, there is no compelling evidence that initiation of dialysis based solely on measurement of kidney function leads to improvement in clinical outcomes, including overall mortality. Additionally, in individuals with advanced CKD, particularly the elderly or those with multiple comorbid conditions, the most widely used measure of kidney function, serum creatinine–based eGFR, may be misleading due to the dependence of serum creatinine on creatinine generation from muscle mass. Accordingly, in otherwise asymptomatic individuals, there is no reason to begin maintenance dialysis solely based on a serum creatinine or eGFR value. Rather, in patients with advanced CKD without clear uremic symptoms, efforts should be directed at preparing patients for a seamless and safe transition to KRT. This includes determining

Table 2. Summary Data From Observational Studies That Assessed the Association Between Serum Creatinine–Based Estimates of Kidney Function at the Time of Initiation of Dialysis and Risk for Death

Study	Sample Size	Study Site	Study Period	Measure of Kidney Function	HR (95% CI) for Association of Kidney Function at Time of Dialysis Initiation With Death Risk
Fink[64] (1999)	5,388	Veterans Affairs, Maryland, USA	04/1995-12/1996	Scr	For every 1-mg/dL higher Scr: 0.96 (0.93-0.99)
Traynor[65] (2002)	235	Glasgow, UK	1987-2000	Cockcroft-Gault CL_{cr}	For every 1-mL/min higher CL_{cr}: 1.11 (1.01-1.21)
Beddhu[66] (2003)	2,920	Dialysis Morbidity and Mortality Study, USA	1996-1997	eGFR by MDRD Study equation	For every 5-mL/min/1.73 m^2 higher eGFR: 1.14 (1.06-1.22)
Kazmi[67] (2005)	302,287	USRDS	1996-1999	eGFR by MDRD Study equation	For eGFR > 10 (reference, <5) mL/min/1.73 m^2: 1.42
Sawhney[68] (2009)	7,299	Canada and Scotland	2000-2005	eGFR by MDRD Study equation	For eGFR > 15 and 10-15 (reference, 5-10) mL/min/1.73 m^2: 1.65 (1.39-1.95) and 1.37 (1.19-1.59), respectively
Stel[69] (2009)	6,716	Europe	2003	eGFR by MDRD Study equation	For every 1-mL/min/1.73 m^2 higher eGFR: 1.02 (1.01-1.04)
Evans[70] (2011)	901	Sweden	05/1996-05/1998	eGFR by MDRD Study equation	For eGFR > 7.5 (reference: <7.5) mL/min/1.73 m^2: 0.84 (0.64-1.10)
Hwang[71] (2010)	23,551	Taiwan	07/2001-12/2004	eGFR by MDRD Study equation	For quintile 5 eGFR (>6.52 mL/min/1.73 m^2) (reference, quintile 1, <3.29 mL/min/1.73 m^2): 2.44 (2.11-2.81)
Lassalle[72] (2010)	11,685	France	2002-2006	eGFR by MDRD Study equation	For every 5-mL/min/1.73 m^2 higher eGFR: 1.09 (1.05-1.14)
Wright[73] (2010)	895,293	USRDS	01/1995-09/1996	eGFR by MDRD Study equation	For eGFR > 15 and 10-15 (reference, 5-10) mL/min/1.73 m^2: 1.44 (1.43-1.45) and 1.15 (1.15-1.16), respectively
Grootendorst[74] (2011)	569	Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)	1997-2005	eGFR by MDRD Study equation	For highest tertile of eGFR (reference: lowest tertile): 1.4 (1.0-1.9)
Rosansky[75] (2011)	81,176	USRDS (nondiabetics, aged 45-64 y)	1995-2006	eGFR by MDRD Study equation	For eGFR > 15.0 and 10.0-14.9 (reference, < 5) mL/min/1.73 m^2: 1.74 and 1.47, respectively
Crews[76] (2014)	84,654; propensity-matched: 61,930	USRDS (aged ≥ 67 y, ≥2 y of prior Medicare coverage)	2006-2008	eGFR by MDRD Study equation	For eGFR ≥ 10 (reference, <10) mL/min/1.73 m^2: 1.11 (1.08-1.14) for propensity-matched analyses
Crews[77] (2014)	652 (187 initiating dialysis)	Cleveland Clinic	2005-2009	eGFR by MDRD Study equation	For eGFR ≥10 (reference, <10) mL/min/1.73 m^2: OR, 0.85 (0.65-1.11) for inverse probability–weighted analyses
Jain[78] (2014)	8,047 initiating PD	Canadian Organ Replacement Register	2001-2009	eGFR by MDRD Study equation	For eGFR > 10.5 and 7.5-10.5 (reference, <7.5) mL/min/1.73 m^2: adjusted HRs of 1.08 (0.96-1.23) and 0.96 (0.86-1.09), respectively

Abbreviations: CI, confidence interval; CL_{cr}, creatinine clearance; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; OR, odds ratio; PD, peritoneal dialysis; Scr, serum creatinine; UK, United Kingdom; USA, United States; USRDS, US Renal Data System.

Table 3. Summary Data From Observational Studies That Assessed the Association Between Measured Kidney Function at the Time of Initiation of Dialysis and Risk for Death

Study	Sample Size	Study Site	Study Period	Measure of Kidney Function	HR (95% CI) for Association of Kidney Function at Time of Dialysis Initiation With Death Risk
Bonomini[79] (1985)	340	Single Italian center		CL_{cr}	12-y survival in early dialysis group: (mean CL_{cr}, 12.9 mL/min), 77%; late dialysis group (mean CL_{cr}, 2.1 mL/min): 51%; no adjustment made for differences in patient characteristics
Tattersal[80] (1995)	63	Single UK center	1991-1992	Renal Kt/V_{urea}	Mean renal Kt/V_{urea} lower in 6 individuals who died; no adjustment made for differences in patient characteristics
Churchill[81] (1997)	680	Canadian-USA Study on Adequacy of Peritoneal Dialysis (CANUSA)	9/1990-12/1992	24-h mean of urinary urea clearance and CL_{cr}	For every 5-L/wk higher mGFR: 0.95 (0.91-0.99)
Beddhu[66] (2003)	1,072	Dialysis Morbidity and Mortality Study, USA	1996-1997	Assumed 24-h urinary CL_{cr}	For every 5-mL/min higher CL_{cr}: 0.98 (0.86-1.14)
Grootendorst[74] (2011)	569	Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)	1997-2005	24-h mean of urinary urea clearance and CL_{cr}	Highest tertile of mGFR (reference: lowest tertile of mGFR): 1.0 (0.7-1.3)

Abbreviations: CI, confidence interval; CL_{cr}, creatinine clearance; HR, hazard ratio; mGFR, measured glomerular filtration rate; UK, United Kingdom; USA, United States.

whether the individual is an appropriate candidate for kidney transplantation and/or maintenance dialysis, providing education about different dialysis therapies, offering decision support for selection of dialysis modality (including conservative care without dialysis), facilitating placement of permanent access, and starting dialysis in a timely manner.[27] Second, maintenance dialysis should not be denied to individuals with kidney failure who may potentially benefit from KRT, such as

Table 4. Commonly Used Validated GFR Estimating Equations in Adults

Coefficient	MDRD Study Equation[82,83] Scr	CKD-EPI Equations Scr (Levey et al,[84] 2009)	CKD-EPI Equations Scys (Inker et al,[85] 2012)	CKD-EPI Equations Scr and Scys (Inker et al,[85] 2012)
Scr	$Scr^{-1.154}$	—	—	—
Scr, when >0.9 mg/dL for men or >0.7 mg/dL for women	—	$Scr^{-1.209}$ if male	—	$Scr^{-0.601}$
Scr, when ≤0.9 mg/dL for men or ≤0.7 mg/dL for women	—	$Scr^{-0.329}$ if male $Scr^{-0.411}$ if female	—	$Scr^{-0.248}$ if male $Scr^{-0.247}$ if female
Scys, when >0.8 mg/dL	—	—	$SCysC^{-1.328}$	$Scys^{-0.711}$
Scys, when ≤0.8 mg/dL	—	—	$SCysC^{-0.499}$	$Scys^{-0.375}$
Age, in years	$Age^{-0.203}$	0.993^{age}	0.996^{age}	0.995^{age}
Female sex	0.742	1.018	0.932	0.969
Black race	1.212	1.159	—	1.08

Note: For the MDRD Study equation, the coefficient of −1.154 for the exponent of Scr indicates that estimated GFR is 1.154% lower for each 1% higher Scr. For any value of Scr, older age and female sex are associated with lower Scr-based estimated GFR, and African American race is associated with higher Scr-based estimated GFR. For the CKD-EPI equations, Scr is modeled as a 2-slope spline with sex-specific knots; Scys is modeled as a 2-slope spline with the same knot for both sexes. The slopes are steeper above than below the knots. Because of the sex-specific knots for the Scr coefficients, the sex coefficients in the CKD-EPI Scr and Scr-Scys equations are not comparable to the MDRD Study equation and the Scys-based CKD-EPI equation. The corresponding sex coefficients for the CKD-EPI Scr and Scr-Scys equations would be 0.75 and 0.83 for Scr values ≥ 0.9 mg/dL, respectively. Conversion factor for Scr in mg/dL to mmol/L, ×388.4.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; Scr, serum creatinine (in mg/dL); Scys, serum cystatin C (in mg/dL).

Adapted with permission of the National Kidney Foundation from Levey et al.[55]

Table 5. Clinical Settings Affecting Creatinine Generation

Setting	Effect on Serum Creatinine
Demographic characteristics	
Older age	Decreased
Female sex	Decreased
African American[a]	Increased
Hispanic[a]	Decreased
Asian[a]	Decreased
Clinical characteristics	
Muscular habitus	Increased
Rhabdomyolysis	Increased
Loss of muscle (amputation, neuromuscular diseases, cachexia)	Decreased
Cirrhosis/advanced liver disease	Decreased[b]
Protein-energy wasting/inflammation	Decreased
Dietary characteristics[c]	
Vegetarian/vegan diet	Decreased
High meat diet	Increased

Note: Based on information in Stevens et al.[86]

[a]Relative to white non-Hispanic.

[b]Tubular secretion of creatinine in liver disease may also account for serum creatinine values that overestimate kidney function.[87]

[c]Creatine supplements may artificially increase serum creatinine (eg, athletes).

Box 4. Symptoms and Signs of Uremia

Symptoms
- Fatigue
- Lethargy
- Confusion
- Anorexia
- Nausea
- Alterations in senses of smell and taste
- Cramps
- Restless legs
- Sleep disturbances
- Pruritus

Signs
- Seizures/change in seizure threshold
- Amenorrhea
- Reduced core body temperature
- Protein-energy wasting
- Insulin resistance
- Heightened catabolism
- Serositis (pleuritis, pericarditis)
- Hiccups
- Platelet dysfunction
- Somnolence

Note: While many other signs and symptoms are associated with advanced kidney failure, many of these are explained at least in part by specific deficits or excesses in hormones, such as anemia and hyperparathyroidism. Although part of the uremic milieu, these are not included in this list. Based on information in Meyer and Hostetter.[61]

individuals with refractory volume overload or refractory hyperkalemia, simply because the GFR is considered "too high."

The statement that the decision to initiate maintenance dialysis should be based upon an assessment of signs and/or symptoms associated with uremia is inherently challenging given the lack of definitive identifiers of uremia.[61] Uremia is a nonspecific constellation of symptoms and signs superimposed on a low GFR (Box 4); accordingly, these symptoms and signs, by definition, can have other causes. Providers need to be aware of uremia "mimickers," especially in the elderly and those receiving poly-pharmacy; the Work Group encourages providers to be diligent in their search for reversible causes of symptoms prior to dialysis initiation. Moreover, at least one cross-sectional comparison suggests that the range as well

as the prevalence of symptoms in patients with advanced CKD and those undergoing HD are similar.[62] This raises the question of which if any of the symptoms commonly present in patients with kidney diseases would be expected to improve with KRT.[63] Conversely, in many patients, the decline in well-being is slow, without a discrete event that could be identified as the "appearance of uremic symptoms." Many patients adapt to lower levels of functioning or to lower levels of dietary intakes or lose weight without being able to acknowledge uremic manifestations. Overall, the Work Group favored an individualized approach to timing dialysis initiation, noting that the current body of data does not allow a prescriptive approach for timing dialysis initiation, a decision which at this time remains within the domain of the "art" of medicine.

Guideline 2: Frequent and Long Duration Hemodialysis

In-center Frequent HD

2.1 We suggest that patients with end-stage kidney disease be offered in-center short frequent hemodialysis as an alternative to conventional in-center thrice weekly hemodialysis after considering individual patient preferences, the potential quality of life and physiological benefits, and the risks of these therapies. (*2C*)

2.2 We recommend that patients considering in-center short frequent hemodialysis be informed about the risks of this therapy, including a possible increase in vascular access procedures (*1B*) and the potential for hypotension during dialysis. (*1C*)

Home Long HD

2.3 Consider home long hemodialysis (6-8 hours, 3 to 6 nights per week) for patients with end-stage kidney disease who prefer this therapy for lifestyle considerations. (*Not Graded*)

2.4 We recommend that patients considering home long frequent hemodialysis be informed about the risks of this therapy, including possible increase in vascular access complications, potential for increased caregiver burden, and possible accelerated decline in residual kidney function. (*1C*)

Pregnancy

2.5 During pregnancy, women with end-stage kidney disease should receive long frequent hemodialysis either in-center or at home, depending on convenience. (*Not Graded*)

BACKGROUND AND DEFINITIONS

Conventional HD remains the most common treatment for end-stage renal disease (ESRD) worldwide and is usually performed for 3 to 5 hours, 3 days per week.[2,88-90] However, some dialysis programs now offer more "intensive" HD regimens, characterized by either longer duration, increased frequency, or both. The Work Group for the KDIGO Controversies Conference on "Novel Techniques and Innovation in Blood Purification" noted that there is no uniform nomenclature to describe the different types of intensive or more frequent HD.[91] Given the multitude of terms in the literature (eg, daily, nocturnal, short daily, daily nocturnal, quotidian, frequent, and intensive), it is often difficult to identify studies

evaluating similar HD prescriptions. Further, the site of therapy, the dialysis prescription, and the level of care often differ. Many patients perform long duration or more frequent sessions themselves at home, while others are fully or partially assisted by nurses or technicians in an outpatient treatment facility. Finally, blood and dialysate flow rates can differ in each of these treatment categories. Such discrepancies may introduce confounding when different HD regimens are compared and these variables are not considered. For these reasons, we believe that the nomenclature in the literature should be unified.

In concordance with the KDIGO Work Group,[91] we suggest that all HD prescriptions specify the duration of the individual dialysis session, the number of treatments per week, blood and dialysate flow rates, the location for HD treatment, and the level of assistance. A proposed nomenclature is summarized in Table 6.

EVIDENCE OVERVIEW

The 2006 guidelines did not contain graded guideline statements regarding frequent HD due to a paucity of evidence.[5,92] In one systematic review conducted prior to the publication of the 2006 guideline, Suri et al[5] identified just 25 studies of short frequent HD (in-center or home) from 1990 to 2006 that included 5 or more adult patients with a follow-up period of at least 3 months, none of which were clinical trials, while Walsh et al,[92] in a second systematic review, found 10 articles and 4 abstracts reporting on long frequent home HD with follow-up of 4 weeks or more, none of which were clinical trials. Short frequent HD improved BP control (10 of 11 studies), improved anemia management (7 of 11 studies), improved serum albumin levels (5 of 10 studies), improved quality of life (6 of 12 studies), saw no change in serum phosphorus level or phosphate-binder dose (6 of 8 studies), and saw no increase in vascular access dysfunction (5 of 7 studies), while long frequent home HD improved BP control (4 of 4 studies), improved anemia management (3 of 3 studies), improved phosphorus levels or decreased phosphate-binder dose (1 of 2 studies), and, in some studies, improved quality of life. In addition, in-center short frequent (daily) HD was associated with high discontinuation rates (Suri et al[5]). Both reviews highlighted serious methodological limitations of the then-existing literature on frequent HD, including small sample sizes, short follow-up time, non-ideal control groups, bias, and little information on potential risks.

Table 6. Descriptive Nomenclature for Various HD Prescriptions

Proposed Name	Time of Day	Duration (h/session)	Frequency (sessions/wk)
Conventional HD	Daytime	3-5	3-4
Frequent HD[a]			
Short	Daytime	<3	5-7
Standard	Daytime	3-5	5-7
Long	Nighttime	>5	5-7
Long HD[b]			
Long thrice weekly	Nighttime or daytime	>5	3
Long every other night	Nighttime	>5	3.5
Long frequent	Nighttime	>5	5-7
Treatment Location			
In-center	Outpatient treatment in a hospital or dialysis facility		
Home	HD treatment in the patient's home		
Level of Assistance			
Fully assisted	HD treatment is performed entirely by a health care provider		
Partially assisted	The patient performs some (but not all) aspects of the HD treatment him or herself (eg, cannulation of fistula, connection/disconnection, setting machine, monitoring blood pressures), while other aspects are performed by a health care provider		
Self-care (with or without an unpaid caregiver)	The patient performs all aspects of the HD treatment him or herself, with no assistance from a health care provider; this may be done with or without the assistance of an unpaid caregiver		
Blood flow rate			
Standard	≥300 mL/min		
Low flow	<300 mL/min		
Dialysate flow rate			
Standard	≥500 mL/min		
Low flow	<500 mL/min		

Abbreviation: HD, hemodialysis.

[a]Short and standard daily HD are usually delivered in-center, while long-nocturnal HD is usually delivered at home.

[b]Long−thrice weekly HD may be delivered in-center or at home, while long every other night and frequent HD are usually delivered at home.

The studies cited in the reviews by Suri and Walsh were the main evidentiary basis for the clinical practice recommendations in the 2006 HD guideline updates.[7]

Since that time, 3 parallel-arm RCTs of frequent HD have been completed: the Frequent Hemodialysis Network (FHN) Daily (short frequent HD in-center) and Nocturnal (long frequent HD at home) trials, and the Alberta Nocturnal (long frequent HD at home) Hemodialysis Trial (Table 7).[8,9,11] The statements on frequent HD in the current guideline are mostly based on the results from these 3 trials. As these randomized trials had low statistical power to detect mortality differences due to small sample size, matched observational studies examining mortality with frequent HD were also reviewed for this update.[93-96] Finally, we also included case reports and case series of outcomes during pregnancy with frequent HD, given the importance of this topic.[97,98] It is important to note that the ERT and Work Group did not review evidence concerning home dialysis modalities with newer technologies using lower dialysate flow rates given the paucity of evidence for this type of home frequent dialysis at the time of review, and the provided recommendations cannot be extrapolated to these newer devices.

RATIONALE FOR GUIDELINES 2.1 AND 2.2

To date, just 1 randomized trial of short frequent HD has been completed.[9] The Work Group is unaware of any randomized trials of home short frequent HD and thus the group developed guideline statements only for in-center short frequent HD.

The FHN Daily Trial randomized 245 patients to receive in-center short frequent HD (1.5-2.75 hours, 6 days per week, minimum target equilibrated Kt/V [eKt/Vn] of 0.9 per treatment, where $Vn = 3.271 \times V^{2/3}$) or in-center conventional HD (minimum target eKt/V of 1.1, session length of 2.5-4 hours). Patients were followed up for 1 year on the assigned treatment. Two co-primary outcomes were compared: the composite of death or change in left ventricular mass, and death or health-related quality of life, as well as 9 prespecified secondary surrogate outcomes. The main study was not powered to examine mortality or other

Table 7. Summary: Randomized Trials of More Frequent HD

Trial Name	HD Intervention	Frequency (d/wk)	Time (h/session)	Qb (mL/min)	Qd (mL/min)
FHN Daily[9]	Short frequent in-center	5.2 ± 1.1	2.57 ± 0.42	396 ± 42	747 ± 68
	Conventional	2.9 ± 0.4	3.55 ± 0.47	402 ± 41	710 ± 106
FHN Nocturnal[8]	Long frequent at home	5.1 ± 0.8	6.32 ± 1.03	262 ± 61	354 ± 106
	Conventional	2.9 ± 0.2	4.26 ± 1.08	350 ± 49	554 ± 126
Alberta Nocturnal[11]	Long frequent at home	5 to 6	≥6 h prescribed	≤250 prescribed	~300 mL/min prescribed
	Conventional	3	Not reported	Not reported	Not reported

Note: Except for the Alberta Nocturnal trial, values given as mean ± standard deviation.
Abbreviations: FHN, Frequent Hemodialysis Network; HD, hemodialysis; Qb, blood flow rate; Qd, dialysate flow rate.

hard outcomes such as hospitalizations, although mortality data are available for extended follow-up participants after they completed their assigned interventions (see description below). The Work Group is unaware of any randomized trials of home short frequent HD and thus the group developed guideline statements only for in-center short frequent HD. In addition, some forms of home short frequent HD are performed using a much lower dialysis flow rate than the dialysate flow rate used in the FHN Daily Trial, thus further limiting the possibility of generalizing FHN Daily trial data to this form of home short frequent HD.

In-center short-frequent HD resulted in statistically significant improvements in health-related quality of life and several surrogate outcomes. Patients receiving in-center short frequent HD demonstrated a mean adjusted increase of 3.4 ± 0.8 points in the RAND-36 Physical Health Composite score, compared to a mean adjusted increase of 0.2 ± 0.8 for patients receiving conventional HD (mean difference, 3.2; $P = 0.004$).[9] In addition, in-center short frequent HD resulted in statistically significant reductions in left ventricular mass, intradialytic systolic BP, antihypertensive medications, serum phosphorus, and use of phosphate binders. Mean differences in these variables (frequent minus conventional groups) were: −13.8 g, 10.1 mm Hg, −0.64 medications per day, −0.46 mg/dL, and −1.35 g equivalent phosphate-binder doses per day).[9,99,100] On the other hand, there were no improvements in serum albumin levels,[101] cognitive function as measured by the Trailmaking Test Part B,[102] depression as measured by the Beck Depression Inventory, mental health as measured by the mental health composite of the RAND,[103] or objective measures of physical performance.[104] Hemoglobin levels decreased by a mean of 0.29 mg/dL in the conventional group compared to a stable hemoglobin level in the more frequent group ($P = 0.03$), while there was no difference in doses of erythropoiesis-stimulating agents (ESAs).[105]

The FHN Daily Trial also identified certain risks associated with in-center short frequent HD. Compared with patients receiving conventional HD, patients randomized to in-center short frequent HD had a statistically significant increased risk of vascular access repairs (hazard ratio [HR], 1.68; 95% confidence interval [CI], 1.13-2.51; $P = 0.01$), primarily driven by increased vascular access repairs in the subgroup of patients with AV accesses at baseline.[106] All types of repairs appeared to be more prevalent with frequent compared to conventional HD, including angioplasties, thrombectomies, and surgical revisions. Infection events were too few to draw conclusions. Access losses were not different between frequent and conventional dialysis groups, but excess losses were likely prevented by appropriate procedures to salvage problem accesses. The effect of frequent HD on catheters was inconclusive as analysis of this subgroup lacked statistical power.

Other adverse outcomes were also examined. Compared with patients receiving conventional HD, more patients randomized to in-center short frequent HD had hypotensive episodes during dialysis ($P = 0.04$).[9] The implications of this are unknown, and the mechanisms underlying this phenomenon are unclear. In-center short frequent HD had no effect on perceived caregiver burden.[15] The effects of in-center short frequent HD on residual kidney function (Kru) loss could not be examined, as patients entering the FHN Daily Trial were selected for minimal Kru at baseline. Finally, adherence to the therapy was moderate, with 77.7% of patients receiving >80% of their prescribed treatments, suggesting that patient burnout is an important consideration.[9]

The main study was not powered to examine mortality alone or other hard outcomes such as hospitalizations, although there are data on mortality from extended follow-up for some participants after they completed their assigned interventions.[107] Of 245 patients randomized in the Daily Trial, 15 died during the first year (5 frequent, 10 conventional). At the end of the 1-year intervention period, 90% of patients randomized to daily HD reverted to 3 or 4 times per week HD. During the extended follow-up period of 2.7 years, using intention-to-treat analysis, there were 16 deaths in the daily HD arm and 25 deaths in the conventional arm. The overall relative

hazard of mortality (short frequent vs conventional) was 0.54 (95% CI, 0.32-0.93; $P = 0.024$); after censoring transplants, the relative hazard was slightly attenuated: 0.60 (95% CI, 0.34-1.05; $P = 0.07$). The investigators cautioned that these results should be interpreted cautiously given that almost all short frequent dialysis patients reverted to conventional dialysis after the 1-year intervention, and statistical power was limited by relatively few deaths. These results have not yet been published in article form.

Three retrospective observational studies evaluated the effect of in-center frequent HD on mortality.[93,94,96] Kjellstrand et al[93] found significantly lowered mortality for European patients receiving in-center short frequent HD, but this analysis did not adjust for known confounders, including ESRD duration and comorbid conditions. Moreover, the comparator group was from the United States, where HD mortality rates are known to be higher than for Europe.[108] In contrast, using registry data from Australia and New Zealand, Marshall et al[94] found no significant mortality difference between in-center frequent HD patients and appropriately matched controls, while Suri et al[96] found that patients receiving in-center short frequent HD were more likely to die. Despite rigorous methodology, these 2 latter studies also have methodological limitations. Marshall et al used an as-treated analysis and did not adjust for duration of end-stage kidney disease. The study by Suri et al may be limited by potential residual confounding; patients receiving daily in-center HD could have been selected because 3-times-weekly HD was inadequate for their clinical condition. Considering all the evidence, the effect of in-center short frequent HD on survival remains uncertain.[109-111]

In summary, because of the controversial and limited evidence regarding the effects of in-center short frequent HD on hard outcomes, the Work Group was unable to make definitive recommendations regarding the use of this therapy in all patients. However, the committee recognized the value of health-related quality of life as a clinically important patient-centered outcome, and that the magnitude of benefit for patients treated with in-center short frequent HD in the FHN Daily Trial was large.[112] In addition, the physiologic benefits of in-center short frequent HD demonstrated in the FHN Daily Trial were thought to be of considerable importance. The Work Group thus thought that patients should have the option to choose in-center short frequent HD over conventional HD if they prefer, forming the basis of Recommendation 2.1. The emphasis on preference was made in recognition of the fact that <10% of patients screened were eligible and agreed to participate in the FHN Daily trial, and adherence to 6 days per week therapy during the 12 month trial period was

moderate. Recommendation 2.2 was based on the importance of the adverse events identified in the FHN Daily Trial. As these recommendations were mostly based on a single randomized trial of 245 patients, the evidence was graded as B to C. The Work Group also recognizes that cost or staffing considerations may affect the ability of an individual dialysis center to provide in-center short frequent HD. Finally, these recommendations do not apply to short home HD therapies or to dialysis prescriptions that are substantially dissimilar (eg, slow dialysate flow rates) to the FHN Daily Study prescriptions.

Research Recommendations

➢ To determine the effect of in-center and home short frequent HD on mortality and hospitalizations
➢ To determine the mechanisms responsible for AV access complications in patients undergoing in-center and home short frequent HD
➢ To gather more robust data regarding the optimal type of vascular access for in-center and home short frequent HD
➢ To determine the mechanisms responsible for hypotension during in-center and home short frequent HD in order to develop appropriate treatments and/or prevention measures
➢ To determine the implications of intradialytic hypotension in the context of in-center and home short frequent HD on patient quality of life and morbidity
➢ To measure the rate of loss of Kru in new patients starting in-center and home short frequent HD
➢ To identify factors responsible for lack of long-term adherence to in-center and home short frequent HD

RATIONALE FOR GUIDELINES 2.3 AND 2.4

Despite their popularity, there is no randomized trial evidence for the efficacy of in-center long HD therapies done 3 days or 3 nights per week or every other day or night dialysis. There are 2 randomized trials that evaluated long frequent HD performed at home 5 to 6 nights per week, compared to conventional home HD (Alberta Trial and the FHN Nocturnal Trials).[8,11] (See Table 6 for the dialysis prescription during the intervention arm in each trial.) Unfortunately, results from these trials were equivocal due to very small sample sizes (Alberta Trial, N = 52; FHN Nocturnal Trial, N = 87).[8,11] Both trials demonstrated statistically better BP and phosphate control with home long frequent HD, but no improvement in anemia.[99,100,105,113] In both studies, the decline in phosphorus levels was so impressive that the dialysis had to be supplemented with phosphorus in 42% of FHN participants and 8% of participants in the Alberta study to prevent

hypophosphatemia.[114] Left ventricular mass improved significantly in the Alberta Trial (mean difference of 15.3 g; $P < 0.05$), with a nonsignificant improvement in the FHN Nocturnal Trial (mean difference of 10.9 g; $P = 0.09$).[99,113] No effect on health-related quality-of-life measures was seen in either trial.[113]

In the FHN Nocturnal Trial, there was no demonstrated improvement with home long frequent HD in measures of cognitive function, depression, or nutrition, while in a subset of participants in the Alberta trial, serum albumin levels improved in nocturnal participants and declined in conventional HD participants.[101-103,113,115]

Similar to in-center short daily HD, risks were also identified in patients treated with home long frequent HD in the FHN Nocturnal Trial.[106] A trend to increased risk of vascular access repairs was not statistically significant likely due to low statistical power, but the magnitude of risk with AV fistulas or grafts was similar to that seen in the FHN Daily Trial (HR, 2.29; 95% CI, 0.94-5.59; $P = 0.07$). Use of the buttonhole technique was associated with a longer period between successive AV access events compared to the rope-ladder technique (HR, 0.44; 95% CI, 0.20-0.97; $P = 0.04$), but infection events were too few to evaluate. Also of note was a statistically and clinically significant accelerated loss of Kru in the long frequent HD arm.[16] In the long frequent group, urine volume declined to zero in 67% of patients by 12 months, compared with 36% in controls. A faster decline in kidney function, as measured by clearance of urea, creatinine, or the mean of the 2, was observed in patients treated with nocturnal compared to conventional dialysis.[16] Since Kru is one of the most important favorable prognostic indicators in patients with end-stage kidney disease, this adverse effect of home long frequent HD may have significant implications. Compared with those randomized to conventional home HD, those randomized to home long frequent HD experienced a trend to an increase in the burden they perceived on their unpaid caregivers; this was statistically significant after multiple imputation.[15] Finally, adherence rates were low to moderate with home long frequent HD.

A third randomized trial, the ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly) Study, has recently reported results in abstract form.[117] In this trial, conducted in Australia, New Zealand, China, and Canada, 200 participants were randomized to either extended (>24 hours per week) or standard (target 12-15 hours per week) dialysis and were followed up for 12 months. Patients could receive treatment either in-center or at home. The primary study outcome, quality of life, was similar in both groups at study end (mean difference in EQ-5D, 0.038; 95% CI, −0.03 to 0.11; $P = 0.27$). There was no difference in systolic BP between groups; however, participants randomized to extended dialysis received fewer BP-lowering agents (mean difference, −0.35 agents; 95% CI, 0.62 to −0.08; $P = 0.01$). Randomization to extended hours was associated with a higher hemoglobin level and lower potassium and phosphate levels during follow-up (respective differences, 3.51 g/L [95% CI, 0.21-6.81; $P = 0.037$]; −0.28 mmol/L [95% CI, −0.43 to −0.14; $P = 0.0001$]; −0.17 mmol/L [95% CI, −0.27 to −0.06; $P = 0.002$]). There were 5 deaths in the extended arm and 2 in the standard arm. The numbers of patients with adverse vascular access events were similar in the 2 arms.

The effect of long frequent HD on mortality is not clear. Two large observational studies suggested improved mortality with home long frequent HD, but these studies are inconclusive as they may be confounded by selection of healthier patients to undergo home long frequent HD therapy at home.[118,119] A third study comparing home intensive (including short frequent, long thrice weekly, and long frequent HD) with home conventional HD found no difference in mortality.[94]

Another study found that survival with home long frequent HD was similar to that with deceased donor transplantation,[120] but this study was confounded by the comparison of Canadian with US patients. This study's findings were refuted by the same authors some years later with a newer analysis showing that all types of kidney transplantation had superior survival compared to home long frequent HD.[121] Preliminary data from extended follow-up of participants in the FHN Nocturnal Trial showed no survival benefit, and possibly an increase in mortality with home long frequent HD.[116] It is difficult to interpret these mortality data given the high nonadherence rate with home long frequent treatment, as well as the large percentage of crossovers in both arms after the main trial ended.[116] Additional data on causes of death and hospitalization in this extended follow-up period have not yet been reported.

In summary, given inconclusive data regarding efficacy, and potentially increased risk of harm and mortality, no firm recommendations regarding home long frequent HD could be made by the Work Group. However, a high value was placed on patient autonomy and potential lifestyle benefits that home long HD (either 3-4 or 5-6 nights per week) may offer, and thus an ungraded statement (2.3) was made to consider these therapies if patients desire them. In contrast, a strong recommendation (2.4) was made regarding the potential risks of home long frequent HD given those observed in the FHN Nocturnal Trial as described in detail above.

Research Recommendations

➢ To determine the effect of home long frequent HD therapies (3-6 nights per week) on mortality and hospitalizations
➢ To gather more robust data regarding the optimal type of access for home frequent HD and the type of cannulation technique for home HD patients
➢ To determine the clinical implications of accelerated loss of Kru that occurs with home long frequent HD
➢ To validate the increased burden on caregivers perceived by patients receiving home long frequent HD by comparison with the actual burden as perceived by caregivers
➢ To develop methods to ameliorate caregiver burden associated with home long frequent HD
➢ To identify factors governing long-term adherence to home long frequent HD

RATIONALE FOR RECOMMENDATION 2.5

There are no randomized trials examining optimal dialysis duration and frequency in pregnancy, and likely there never will be due to the small number of patients available for enrollment, as well as lack of perceived equipoise. Given that many nephrologists prescribe long and frequent HD for pregnant women with end-stage kidney disease, and given the importance of this issue, the committee decided to consider observational evidence on this topic. This topic was not reviewed by the ERT and is thus based solely on the review and interpretation of this literature by the Work Group.

Pregnancy in women with end-stage kidney disease is not common, but women who conceive while undergoing conventional HD have very high rates of neonatal complications, including miscarriage, stillbirths, prematurity, and small-for-gestational-age births.[122,123] Live birth rates with conventional HD (weekly dialysis time of 15-24 hours for most reports) are estimated to be in the range of 50% to 87%.[122]

Several case-series have suggested that pregnancy-related outcomes might be improved with longer, more frequent HD treatments.[124,125] During a Canadian study of in-center long frequent HD, 22 pregnant women who received a weekly HD time of 48 ± 5 hours at least 6 nights per week carried their pregnancies to a mean of 36 weeks, with an 86% live birth rate and mean birth weight of $2,118 \pm 857$ g. In comparison, in the American Registry for Pregnancy in Dialysis Patients, the median duration of pregnancy was 27 weeks ($P = 0.002$) with a live birth rate of 61% ($P = 0.03$) and a mean birth weight of $1,748 \pm 949$ g.[98] A rough dose-response between dialysis intensity and pregnancy outcomes was noted in the Canadian cohort, with live birth rates of 48% in woman dialyzed for 20 or fewer hours per week, 75% in women dialyzed for 30 hours per week, and 85% in women dialyzed for more than 36 hours per week.

The Work Group discussed this topic at great length, and opinions differed widely with respect to what type of statement should be made. On one hand, all members placed a high value on the avoidance of neonatal and maternal complications. Further, most indicated that they themselves would not be comfortable offering women with end-stage kidney disease less than 6-times-weekly therapy. They also recognized that strong evidence in the form of RCTs to definitively determine the effect of frequent versus conventional HD on pregnancy outcomes is unlikely to ever be available due to small numbers and lack of perceived clinical equipoise. Given these considerations and based on the observational reports described above, some thought that a strong recommendation should be made to use long frequent HD over conventional HD in pregnant women with end-stage kidney disease. However, the majority of members thought that the evidence base was too weak to support a recommendation, and thus an ungraded statement was made.

Research Recommendations

➢ To obtain better estimates of the risk of pregnancy-related complications with conventional HD versus long frequent HD

Guideline 3: Measurement of Dialysis—Urea Kinetics

3.1 We recommend a target single pool Kt/V (spKt/V) of 1.4 per hemodialysis session for patients treated thrice weekly, with a minimum delivered spKt/V of 1.2. (*1B*)

3.2 In patients with significant residual native kidney function (Kru), the dose of hemodialysis may be reduced provided Kru is measured periodically to avoid inadequate dialysis. (*Not Graded*)

3.3 For hemodialysis schedules other than thrice weekly, we suggest a target standard Kt/V of 2.3 volumes per week with a minimum delivered dose of 2.1 using a method of calculation that includes the contributions of ultrafiltration and residual kidney function. (*Not Graded*)

RATIONALE

Target Dose (Guideline 3.1)

This guideline is unchanged from the previous guideline. Small-solute clearance is currently considered the best measure of HD and its adequacy. Kt/V, the fractional urea clearance, is the most precise and tested measure of the dialyzer effect on patient survival and is the most frequently applied measure of the delivered dialysis dose. The difference between the minimum and the target dose is based on a within-patient coefficient of variation in the HEMO (Hemodialysis) Study of ∼10% and is designed to limit the number of treatment doses that fall below the minimum as explained in the previous KDOQI guidelines.[7]

Evidence for the Importance of Small-Solute Clearance

Although admittedly a crude correlate with clinical outcomes, patients cannot survive without adequate small-solute clearance. This in an inescapable conclusion derived from the successful prolongation of life by HD, and especially in the early era when membranes removed few or no large-molecular-weight solutes. Although the concentration of each retained toxic solute is likely the proper target of HD dosing (concentration-dependent toxicity), measurement of any selected representative solute is confounded by its generation (or appearance) rate. The generation rate of a single solute may vary and stray from the generation rate of other important toxic solutes, effectively disqualifying the selected solute's concentration as nonrepresentative. Similarly, measurement of a representative solute's removal rate is ultimately, in a steady state of mass balance, a measure only of its generation rate. However, the ratio of the removal rate to the solute concentration, defined as solute clearance, is a genuine measure of the dialysis solute purging effect and tends to be constant among similar small solutes, independent of the various solute generation rates and concentrations. Selection of a marker solute to measure clearance is therefore more reasonable than a concentration marker because clearance is less encumbered by either the solute's concentration or its generation rate. The ideal representative solute for assessment of clearance should be easily measured and freely move by diffusion through the dialysis membrane and among body compartments without sequestration in remote compartments or binding to macromolecules in the serum. Urea is currently the best representative small solute because of its abundance and close compliance with the above criteria, as well as the reliability and low cost of urea nitrogen assays. Native kidney function, when present, can be measured as urea clearance and combined with the dialyzer clearance to determine the total effective small-solute clearance.[7]

Evidence for the Importance of Urea Clearance

For intermittent HD, the expression of clearance should include the patient's treatment time (t) and adjustment for patient size. As explained below, the most convenient measure that satisfies these requirements is Kt/V. Several observational studies and 1 controlled clinical trial have shown a strong correlation between urea Kt/V and mortality.[126-128] An additional clinical trial showed no survival benefit at higher levels of Kt/V,[129] but previous studies clearly showed that lower values were strongly associated with increased morbidity and should therefore be avoided.[126,127]

Methods for Measuring Urea Clearance

Urea Kt/V is most conveniently measured using mathematical modeling of the predialysis and postdialysis serum urea concentration.[130,131] This method provides an integrated or average clearance during the entire HD and is patient specific, often called the "delivered HD dose."

The predialysis blood sample must be drawn before injecting saline, heparin, or other potential diluents. The postdialysis blood sample should be drawn from the dialyzer inflow port using a slow-flow method (100 mL/min for 15 seconds) or a stop-dialysate-flow method (for 3 minutes). These measurements should be done at least monthly as recommended in the previous guidelines.[7]

Several methods have been used by laboratories and dialysis clinics throughout the country to calculate Kt/V; these methods include simplified explicit

formulas (see item 1 in Appendix), multicompartment models, and on-line conductivity measurements (see item 5 in Appendix), not all of which generate the same value. An example of errors generated by simplified formulas is shown in Fig 1. Although the urea reduction ratio (URR) is easy to calculate and has been used as a standard to measure the delivered hemodialysis dose,[132] it should be phased out in favor of more precise methods. URR is fraught with errors due to changes in the patient's urea volume (V) and urea generation (G) during HD and inability to incorporate the patient's Kru in the expression of dose (see below).

A reference method against which other methods can be compared to guarantee uniformity and protect patients from underdialysis is available on the web (www.ureakinetics.org).[133] This reference model is an open-source program freely available for nonprofit use and includes calculation of single-pool Kt/V (spKt/V), 2-pool Kt/V, standard Kt/V (stdKt/V)—see below, and surface area–adjusted stdKt/V (SA-stdKt/V) (see item 4 in Appendix).

Small-solute clearance can also be measured directly across the dialyzer from changes in dialysate outflow conductivity in response to pulsed changes in the dialysate inflow concentration (see item 5 in Appendix). Conductivity clearances must be measured several times during each treatment to obtain an average for the entire HD. Methods for calculating Kt/V from conductivity measurements require a correction for cardiopulmonary recirculation[134,135] and an independent measure of V. Advantages of this method include ease of measurement, immediate feedback to the clinician, no need for blood and dialysate sampling for analysis, no disposables (inexpensive), capability of more frequent measurements, and the potential for using surface area as the denominator. Disadvantages include the need for an estimation or measurement of V for comparison with modeled urea Kt/V. At the present time, this and other alternative methods to measure small-solute clearance (eg, monitoring UV absorbance of spent dialysate) can only be used if equivalence to the reference standard noted above can be demonstrated.

Kt/V calculated using the equilibrated postdialysis blood urea nitrogen (BUN) level (eKt/V) is recommended by some as a more accurate determinant of the dialysis effect.[139] Methods used to measure eKt/V require waiting 30 minutes after stopping HD to obtain the postdialysis blood sample, or an alternative mathematical manipulation of the BUN in the immediate postdialysis blood sample. Although seemingly reasonable, these additional maneuvers add complexity and an additional approximation without documented advantage; studies that justify the rationale for this preference are lacking.

For thrice-weekly HD in patients with low residual native kidney clearance (Kru < 2 mL/min), the target spKt/V dose remains 1.4 volumes per dialysis, minimum dose 1.2. This recommendation is unchanged from the previous KDOQI guideline.

Adjustments for Kru (Guideline 3.2)

Importance of Kru

The correlation between Kru and patient survival is strong and consistent among studies (see Fig 2).[140] Although a seemingly small contributor to urea clearance, a Kru value of 3 mL/min in the average patient is equivalent to a stdKt/V value of approximately 1.0 volume per week. In addition, it affords better fluid volume control and a potential benefit from elimination of poorly dialyzed solutes normally secreted by the native kidney.[141,142] Loss of Kru has been postulated as a contributor to the increased mortality observed in patients dialyzed frequently at night.[16,116,143]

Adjustment Methods Include Quarterly Measurements of Kru

Inclusion of Kru in the model of urea kinetics allows an accurate assessment of the urea generation rate from which the patient's protein catabolic rate (PCR) can be determined. If the patient has significant Kru that is not included in the mathematical model, PCR will be significantly underestimated. Acknowledging that collection of urine is a burden that patients resist, the recommendation for quarterly assessments is a
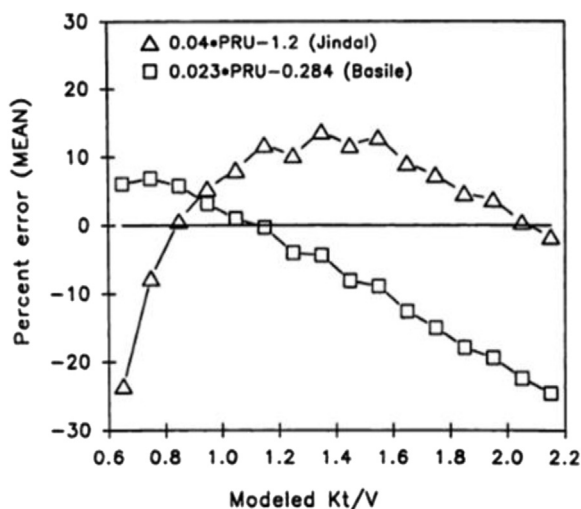

Figure 1. Systematic errors from 2 commonly used linear formulas based on percent reduction in urea concentration (PRU). The formula of Basile et al[136] has less error than the equation of Jindal et al[137] in the usual range, but it overestimates the dose in the critical area of Kt/V < 1.0. Reproduced with permission of the American Society of Nephrology from Daugirdas.[138]
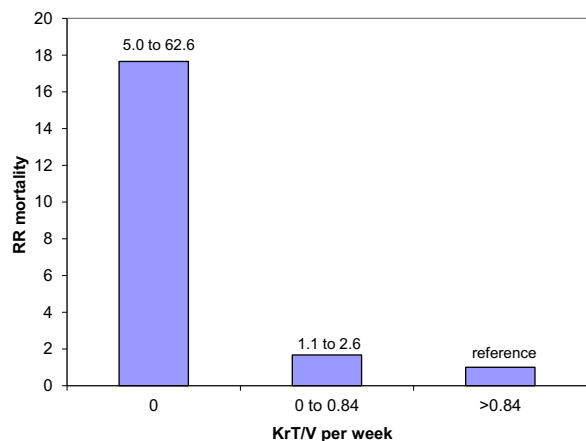
Figure 2. Data from the Netherlands Cooperative Study showing a marked increase in risk of death in patients with no residual native kidney function (KrT/V). Data source: Termorschuizen et al.[140]

compromise. However, if the targeted dialyzer Kt/V has been reduced because of significant Kru, and Kru changes abruptly as indicated by a change in urine volume or risks commonly encountered during hospitalization, an unscheduled measurement should be done to avoid prolonged insufficient dialysis as Kru is lost. In such patients whose dialysis prescription has been modified by Kru, urine volume should be measured monthly.

Current methods for measuring Kru include urine collection for urea and/or creatinine clearance and use of exogenous filtration markers like iothalamate to determine clearance. As stated above, urea is particularly useful as renal and dialysis clearances can be combined using current equations, with the average serum urea concentration during the urine collection estimated from predialysis and postdialysis blood samples or mathematical modeling of the urea concentration profile (see item 2 in Appendix). To combine intermittent Kt/V with Kru, methods have been developed to account for the higher efficiency of continuous Kru compared to intermittent "dialyzer clearance" (see item 4 in Appendix, and both the appendix[7(ppS75-S77)] and clinical practice recommendations for guideline statement 2 in the previous KDOQI guidelines).[7]

HD Schedules Other Than Thrice Weekly (Guideline 3.3)

stdKt/V is the weekly urea generation rate factored by the average predialysis serum urea concentration during the week.[144,145] By definition, it includes the contributions of ultrafiltration during dialysis and Kru.[146] stdKt/V was derived from attempts to account for the improved efficiency of more frequent and continuous dialysis treatments (as well as continuous Kru and PD) compared to less frequent intermittent

HD, and is based on a comparison of achieved average solute concentrations in HD and PD patients. stdKt/V is considered a "continuous equivalent clearance" that allows comparison of continuous with intermittent dialysis and is based on the equivalence of outcomes in patients dialyzed with continuous PD and those treated with thrice-weekly HD.[144,145] A more detailed description of stdKt/V can be found in the previous KDOQI guidelines under clinical practice recommendations for Guidelines 2 and 4.[7] stdKt/V can be estimated from spKt/V using explicit mathematical formulas that include adjustments for weekly ultrafiltration and native Kru (see item 3 in Appendix).[146]

Since both spKt/V and stdKt/V are normalized by V, the patient's urea (water) volume, both are potentially underestimated in small patients and in women. Efforts have been made to eliminate this error by substituting body surface area (BSA) in the denominator and are shown in item 4 in Appendix.[147] BSA is more commonly used as a denominator for physiologic functions, including basal metabolism, cardiac output, and glomerular filtration. Because BSA depends more on height than weight, substitution of BSA for V in the denominator reduces the error when the patient loses weight or gains edema fluid, neither of which should affect the need for dialysis but can cause significant changes in Kt/V.

Limitations of the Guidelines

Studies of average requirements in a population indicate that clinical outcomes are optimized when the patient is treated with the delivered dose of dialysis recommended in these guidelines.[127,129] Since the measure of dose as small-solute clearance is a compromise that acknowledges a lack of knowledge about the specific toxic phenomena caused by loss of kidney function, it is possible and perhaps likely that an occasional patient may generate toxins at a rate well above average and therefore require more dialysis than recommended by these guidelines. Clinicians should be alert to subtle symptoms and signs of kidney failure that may indicate a need for more dialysis or a different dialysis modality. Additional possible indications for more dialysis than recommended by these guidelines are outlined in Guideline 4.

After the immediate life-threatening effects of uremia have been controlled by standard HD, the patient is often left with symptoms and objective disorders that have been lumped together as a "residual syndrome."[130,148] The combined effect of this set of disorders may also account for the relatively high yearly mortality rate observed in the dialysis population. In many cases, relief from specific aspects of the syndrome requires additional treatments, some of which may not yet be available to clinicians. Well-known

aspects include anemia, hyperparathyroidism, pruritus, psychological depression, and protein-energy wasting, all of which may respond to treatments that are independent of dialysis. The underlying cause of the patient's kidney disease (eg, diabetes mellitus or systemic lupus erythematosus) may continue to be active and contribute to the syndrome. Additional causes of the syndrome have been proposed, including the effects of protein carbamylation, retention of protein-bound uremic toxins, some of which are products of the gut microbiome, advanced glycosylation end products, inflammatory mediators, and highly sequestered solutes that are not well removed by standard dialysis.

Research Recommendations

Future research should be directed to better understand the residual syndrome with focus on treatment and improved survival while not losing sight of small-solute removal, which must be considered the most important life-sustaining aspect of HD.

APPENDIX TO GUIDELINE 3

1. Method for estimating spKt/V from the natural logarithm of the postdialysis to predialysis BUN ratio.

A linear equation has been developed and been shown to give reliable results for spKt/V when applied to HD administered 3 times per week[138]:

$$spKt/V = -\ln(R - 0.008 \times T) + (4 - 3.5 \times R) \times 0.55 \times \text{Weight loss}/V$$

R is the ratio of postdialysis to predialysis BUN; V is body water volume and Weight loss is expressed in the same units; and T is treatment time in hours.

However, for other schedules including twice or up to 7 treatments per week, the results stray from Kt/V values assessed by formal urea modeling. The errors are largely due to differences in the effect of urea generation between treatments. A recent change to the above established formula accounts for this variable and effectively eliminates these errors:

$$spKt/V = -\ln(R - GFAC \times T) + (4 - 3.5 \times R) \times 0.55 \times \text{Weight loss}/V\ [149]$$

This equation differs from the above by substitution of GFAC (G factor) for the constant 0.008. GFAC is a term that reduces R to its estimated value in the absence of urea generation and ranges from 0.0045 to 0.0175, depending on the frequency of treatments, but mostly on the preceding interdialysis interval (PIDI). Values can be obtained from a table in the original publication and can be roughly estimated as 0.175 divided by the PIDI in days.

2. Method for estimating Kru from serum samples at the beginning and end of the urine collection period.

BUN concentration fluctuates greatly during and between HD sessions, so the mean or average BUN during the urine collection period must be determined to calculate the clearance. Formal modeling allows a more precise estimate without the need for additional blood sampling, but in the absence of a program to accomplish this, the average BUN can be estimated from BUN measurements at the beginning and end of the urine collection period. The collection period should extend from the end of an HD session to the beginning of the next. As an approximation, the average of the pre- and post-BUN measured during the modeled HD session can be used in the calculation of Kru. Kru can be combined with the dialyzer urea clearance either by adding it directly to stdKt/V as shown below (item 3 in Appendix) or by inflating its value to account for the higher efficiency of continuous clearances, then adding it to spKt/V as outlined in the appendix to the previous KDOQI guidelines.

3. Method for estimating stdKtV from spKt/V.

stdKt/V was conceived by Gotch[145] as a method for downgrading intermittent dialyzer clearances to the equivalent of a continuous clearance by redefining clearance as the urea generation rate (G) divided by the average predialysis BUN (avCpre). The calculation was based on a fixed volume model of urea kinetics during an entire week. The original method was later simplified by Leypoldt[150] and then further enhanced by Daugirdas et al,[146] who included the patient's ultrafiltration rate (Uf) and Kru. As originally defined by Gotch,[145] stdKt/V includes the effects of Uf and Kru. However, when measured using modeled values for G, eKt/V, and avCpre, the contribution of Kru is inappropriately downgraded because G/avCpre assumes that the Kru component also uses the avCpre instead of the average BUN in the denominator. To correct for this error when Kru is included, modeled values for G and V must be used to calculate stdKt/V in the absence of Kru, which can then be added as Kru $\times$ 10,080/V.[146]

The following set of equations allow a reasonable approximation of true stdKt/V from spKt/V with accurate contributions by Uf and Kru.[145,146,150]

$$eKt/V = spKt/V(t/(t + 30))\ [151]$$

$$stdKt/V = \frac{10{,}080 \frac{1 - e^{-eKt/V}}{t}}{\frac{1 - e^{-eKt/V}}{eKt/V} + \frac{10{,}080}{Nt} - 1}$$

(fixed volume model, no Kru)

$$\mathrm{stdKt/V} = \frac{S}{1 - \frac{0.74}{F}\left[\frac{U_f}{V}\right]} + K_r\frac{10{,}080}{V}$$

(variable volume model with Kru)

S is stdKt/V derived from a fixed-volume model (second equation above); N is the number of dialyses per week; U_f is the weekly ultrafiltration volume in mL; V is the volume of urea distribution in mL; Kru is the residual native kidney clearance of urea in mL/min; 10,080 is the number of minutes in a week.

In the absence of Kru, the last equation above gives a value for stdKt/V that is ∼7% higher on average than the preceding equation.

To protect patients from underdialysis, the contribution of Kru should be added only if a measurement has been done within 3 months prior to the modeling date.

4. Method for calculating SAstdKt/V

The volume of urea distribution (V) in the denominator of the urea clearance expression (Kt/V) is problematic. V is conveniently included in the exponential expression of clearance as calculated from simple measurements of pre- and postdialysis BUN, and as a measure of total-body water is closely tied to lean body mass, which is often used to dose drugs. However, the more commonly used denominator for physiologic functions including native kidney function is BSA. A secondary analysis of the HEMO data, which showed improved outcomes in women but not in men treated at the higher HD dose, raised concerns about possible

inappropriate use of V as the dose denominator in women and smaller patients (see Fig 3 below).[147,152] Efforts to eliminate this bias both in women and in smaller patients led to an expression of stdKt/V with BSA in the denominator that retained the current targeted values[146,153,154]:

$$\mathrm{SAstdKt/V} = \frac{\mathrm{stdKt/V}}{20} \times \frac{Vw}{BSA}$$

SAstdKt/V is the surface area–normalized standard Kt/V (fraction/wk); V_W is the patient's volume of urea distribution determined by the Watson formula (L)[155]; BSA is the patient's body surface area based on height and weight (m^2)[156]; and 20 is a normalizing factor (the population mean V/BSA, L/m^2). This normalizing factor may be different from 20 when using equations other then those by Watson et al[155] and DuBois and DuBois[156] to estimate V and BSA, respectively, for example, in children.

5. Method and equations for measuring conductivity dialysance.

$$D = [Qd + Qf][1 - (Co_1 - Co_2)/(Ci_1 - Ci_2)]^{157}$$

Co and Ci are dialysate outlet and inlet conductivities (mS/cm); D is dialysance (mL/min); Qd is dialysate flow; and Qf is ultrafiltration flow.

Dialysance is used here because the inflow conductivity is not zero. In practical terms, conductivity dialysance is a measure of the dialyzer small-solute clearance because the solutes responsible for dialysate conductivity are small (mostly sodium + anion) and easily dialyzed. Conductivity dialysance is highly correlated with urea clearance.[135,157]
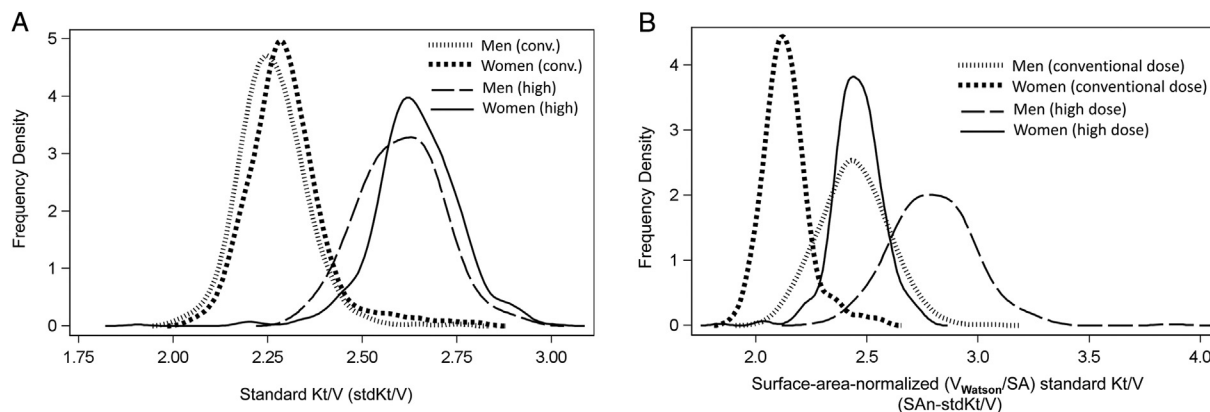

Figure 3. Delivered dialysis doses in the HEMO (Hemodialysis) Study. (A) A clear separation of the delivered dialysis doses expressed as standard Kt/V was achieved for all patients during the HEMO Study. (B) When normalized to BSA, women randomized to the high dose received a dose comparable to the conventional dose in men.[129] Reproduced with permission of the American Society of Nephrology from Daugirdas et al.[147]

Guideline 4: Volume and Blood Pressure Control—Treatment Time And Ultrafiltration Rate

4.1 We recommend that patients with low residual kidney function (< 2 mL/min) undergoing thrice weekly hemodialysis be prescribed a bare minimum of 3 hours per session. (*1D*)

4.1.1 Consider additional hemodialysis sessions or longer hemodialysis treatment times for patients with large weight gains, high ultrafiltration rates, poorly controlled blood pressure, difficulty achieving dry weight, or poor metabolic control (such as hyperphosphatemia, metabolic acidosis, and/or hyperkalemia). (*Not Graded*)

4.2 We recommend both reducing dietary sodium intake as well as adequate sodium/water removal with hemodialysis to manage hypertension, hypervolemia, and left ventricular hypertrophy. (*1B*)

4.2.1 Prescribe an ultrafiltration rate for each hemodialysis session that allows for an optimal balance among achieving euvolemia, adequate blood pressure control and solute clearance, while minimizing hemodynamic instability and intradialytic symptoms. (*Not Graded*)

RATIONALE FOR GUIDELINE 4.1

The optimal duration of each HD session for patients treated thrice weekly remains unknown. In the NCDS (National Cooperative Dialysis Study), the difference in hospitalization rates for patients assigned to different treatment durations did not reach statistical significance ($P = 0.06$).[127] Similarly, in the HEMO Study, a randomized controlled clinical trial evaluating different targets for small-molecule clearance in patients undergoing in-center conventional HD, increasing the HD dose either by increasing the session length or by increasing the dialyzer clearance failed to show meaningful differences in patient outcomes, with no significant benefit in mortality.[129] In the FHN Nocturnal trial, which randomized 87 patients to more frequent treatment and longer treatment times or conventional home HD, more frequent and longer dialysis treatment was not associated with any significant change in left ventricular mass.[11] In contrast, the Canadian nocturnal HD trial demonstrated significant regression of LVH with nocturnal HD.[8] In an older randomized crossover study of 38 patients treated for 2 weeks with 5 versus 4 hours of

dialysis, 5 hours of HD was associated with greater hemodynamic stability and fewer hypotensive episodes, especially among patients older than 65 years,[158] supporting the concept that longer dialysis may have benefits. However, this study also was limited by its small sample size, short length of follow-up, and exclusion of individuals requiring >4 L of ultrafiltration per treatment. The Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial (ClinicalTrials.gov identifier, NCT02019225), an ongoing 3-year pragmatic RCT comparing longer HD treatments (4.25 hours) with conventional HD prescriptions in incident HD patients in the United States (on average, 3.5 hours), should provide further insight.

While there is a paucity of clinical trial data to inform recommendations for optimal length of treatment time, several observational studies have associated shorter HD sessions with higher mortality.[159-161] Importantly, the Work Group could find no evidence to suggest harm from extending treatment times. In a recent observational study of 746 patients using propensity score matching to compare those treated with thrice-weekly in-center nocturnal HD (7.85 hours) or conventional in-center HD (3.75 hours), conversion to nocturnal HD was associated with a 25% reduction in the risk for death after adjustment for age, body mass index, and dialysis vintage (HR, 0.75; 95% CI, 0.61-0.91; $P = 0.004$). Additionally, nocturnal HD was associated with lower BP, lower serum phosphorus, and lower white blood cell count, while interdialytic weight gain, hemoglobin, serum albumin, and calcium were all higher among those treated with nocturnal HD.[109] Of note, the duration of nocturnal sessions in this cohort exceeded the range of times currently in use for patients undergoing conventional in-center HD.

Patients who have shorter treatment times may have more difficulty controlling BP.[162] Conversely, longer HD sessions appear associated with better control of BP, possibly due to achieving better extracellular volume (ECV) control.[163,164] Control of ECV with the combination of dietary sodium restriction and appropriate ultrafiltration with[165] or without[166] low-sodium dialysate has been shown to be effective for BP control and regression of LVH in small uncontrolled studies of patients treated with conventional HD (4-5 hours).[167] These findings remain unconfirmed in larger more contemporary clinical trials. Additional reported benefits of longer treatment times include lower serum phosphorus levels despite higher dietary phosphorus intake and reduced use of phosphate binders.[168]

It was the prior Work Group's opinion that a minimum treatment time of 3 hours reflected contemporary clinical practice and was an especially important threshold level in patients with low Kru (creatinine clearance < 2 mL/min). This opinion was largely based on the treatment time delivered within the standard-dose arm in the HEMO trial (195 ± 23 minutes). Thus, 3 hours was selected as the "bare minimum." Since publication of the prior guideline, increasing evidence suggests that longer treatment times may offer clinical benefits beyond small-solute removal. Despite the opinion of many members of the Work Group who routinely initiate HD for 3.5 to 4 hours, the Work Group did not find sufficient evidence to warrant a change in the minimal treatment time recommendation. However, the Work Group acknowledged that many patients require more than 3 hours to achieve optimal volume and metabolic control and suggested that sodium and water balance, interdialytic weight gain, hemodynamic stability during HD, BP control, overall metabolic control (including ability to manage, eg, metabolic acidosis, serum phosphorus, and potassium), Kru, patient preference, and health-related quality of life also be considered when making a decision regarding HD treatment time. Longer treatment times may be required for patients with high interdialytic weight gain, high ultrafiltration rates, poorly controlled BP, difficulty achieving dry weight, or poor metabolic control.

RATIONALE FOR GUIDELINE 4.2

Although hypertension affects 60% to 90% of HD patients, the clinical benefits of treatment of hypertension in patients undergoing HD have not been established. Observational cohort studies have also been unable to demonstrate evidence for a higher risk of death or CV events in patients undergoing maintenance HD with higher predialysis BPs. In contrast, observational data suggest higher risk of death in patients with low systolic BP, both pre- and post-HD.[169] It is difficult to make treatment recommendations based on these and other observational cohort studies. The inability to demonstrate a higher risk for death with higher BP in these observational studies likely reflects confounding from comorbid conditions like CV disease and protein-energy wasting. In at least one prospective study, higher mean arterial BP was associated with the development of progressive concentric LVH, de novo ischemic heart disease, and de novo congestive heart failure.[170] It is the opinion of the Work Group that control of BP is likely important to reduce the high CV risk of patients undergoing maintenance dialysis. While the ongoing Blood Pressure in Dialysis trial may provide further information about the effects of different BP targets in HD patients on cardiac morphology,[171] the current paucity of clinical trial data does not allow defining the target predialysis, postdialysis, or ambulatory BP for HD patients.

The prevalence and severity of hypertension in patients undergoing maintenance HD is in part attributable to sodium and water retention and ECV expansion.[172-174] No RCTs have tested the hypothesis that one method of BP control is superior to another in improving outcomes, but considering that ECV expansion is an important contributor to elevated BP, it is the opinion of the Work Group that reducing ECV should be the first line of treatment. Achievement of true dry weight, which still remains a largely clinical determination, is necessary for control of BP,[174-177] while failure to achieve target dry weight associates with higher all-cause and CV mortality.[178,179] In one small clinical trial, targeted reduction in ECV using bioimpedance guidance improved BP, LVH, and arterial stiffness when compared to usual-care assessment of dry weight and determination of ultrafiltration rate.[180] However, the effect of controlling BP and reducing LVH on patient-centered outcomes such as hospitalization, CV morbidity, and mortality remains unknown.

To improve control of ECV, reduction of dry weight should be accomplished gradually (over 4-12 weeks or longer) and with assessment of patient tolerability both on and off HD. The Dry Weight Reduction Intervention (DRIP) trial is the largest RCT demonstrating the effect of dry weight reduction on BP control.[181] In this study, 150 HD patients were randomized 2:1 to gradual dry weight reduction (0.1 kg reduction per 10 kg body weight) versus usual care. With an average weight loss of ~1.0 kg, gradual dry weight reduction resulted in an additional ~7 mm Hg greater reduction in ambulatory BP at 8 weeks.[181] However, adverse events including hypotension and seizures were noted with dry weight probing; thus, more gradual reductions may be better tolerated. Critically, whether there is a longer term benefit of this strategy on hard clinical outcomes remains unknown.

The safety and tolerability of the HD procedure is dictated in part by the ultrafiltration rate, which in turn is determined by the interdialytic weight gain and length of each session. No RCTs have tested the hypothesis that reducing interdialytic weight gains or reducing ultrafiltration rates can improve patient-centered outcomes. Observational studies suggest that both large interdialytic weight gain and high ultrafiltration rate are associated with higher mortality.[182-186] Mechanistically, these associations seem plausible, but given the observational nature of these studies, the results may be confounded, especially

because the mortality risk was modest (HR, 1.12-1.29) and only the extremes of interdialytic weight gain (>4.8% of body weight, >5.7% of body weight, ≥4.0 kg, and ≥3 kg, respectively) were associated with adverse outcomes. It should be highlighted that the overall goals of reducing interdialytic weight gain are to try to maximize tolerability of HD and to avoid long-term ECV overload, which is associated with higher CV morbidity and mortality.[187]

Higher ultrafiltration volumes have been shown to be associated with higher odds of myocardial stunning.[188] In addition, HD itself is associated with decreases in myocardial blood flow that are accentuated by ultrafiltration.[189] These data suggest that microcirculatory changes are not solely due to reductions in plasma volume and may be caused by other factors as well.[190] Taken together, the above considerations informed the opinion of the Work Group to recommend minimizing ultrafiltration rates as best possible in order to maximize hemodynamic stability and tolerability of the HD procedure. However, the Work Group did not find sufficient strength of evidence to recommend an absolute threshold for ultrafiltration rate.

An important way to reduce ultrafiltration rates while also achieving optimal control of hypervolemia is to ensure adequate sodium balance. There is evidence to suggest that high dietary sodium intake and inadequate sodium removal during HD can result in excess fluid intake and hypertension. However, there is a paucity of randomized clinical trials upon which to formulate firm guidelines for either dietary sodium intake or individualized dialysate sodium prescriptions. Despite generic dialysis sodium prescriptions being widely utilized, there is increasing debate that a standard 138- or 140-mEq/L dialysate sodium prescription might not be appropriate for all patients.[191] On one hand, high dialysate sodium can lead to inadequate sodium removal during dialysis, resulting in higher interdialytic weight gains and hypertension, necessitating higher ultrafiltration targets, and, if unable to achieve these targets, chronic volume overload. On the other hand, lower sodium dialysate is associated with greater likelihood of hemodynamic instability during HD and thereby may predispose to inadequate fluid removal and subsequent volume overload. A number of small clinical trials, many of which were uncontrolled, have examined the relationship between lowering dialysate sodium and BP (Table 8). Most of these small studies demonstrated that lowering dialysate sodium is associated with reduced BP burden.

As mentioned above, sodium loading during HD clearly results in greater thirst with resultant volume expansion, increased cardiac workload, and subsequent hypertension. Interestingly, recent in vitro studies suggest that exposure to high sodium may result in hypertension independent of its effects on ECV. These studies suggest multiple pathways for elevation of the BP with high plasma sodium concentrations, including but not limited to sympathetic overactivity, increased activity of the renin-angiotensin-aldosterone system (RAAS), and impaired nitric oxide bioavailability.[200-204]

In summary, high sodium diet, volume expansion, and exposure to high-sodium dialysate all result in high BP in HD patients. Large RCTs to show a beneficial effect of lowering the dialysate sodium concentration on CV outcomes are lacking, but one trial in New Zealand (comparing the effect of dialysate sodium concentrations of 135 vs 140 mEq/L on LVH) is ongoing.[205] While observational studies do not suggest benefit associated with lower dialysate

Table 8. Published Clinical Studies on the Effect of Lowering Dialysate Sodium on Subsequent BP

Reference	N	Dialysate Na Change, mEq/L	BP Effect	Comments
Krautzig[165]	8	140 → 135	Decreased	Also dietary Na restriction and fixed Na decrease
Farmer[192]	10	138-140 → 133-135	Decreased	Fixed decrease in Na, ambulatory BP measured
Kooman[193]	6	140 → 136	NS	Fixed decrease in Na
Ferraboli[194]	14	140 → 135	Decreased	Fixed decrease in Na
De Paula[225]	27	138 → 135	Decreased	Tailored decrease in Na
Lambie[195]	16	136 → variable	Decreased	Progressive titration in Na based on dialysate conductivity
Sayarlioglu[196]	18	Variable based on predialysis Na	Decreased	Decreased inferior vena cava diameter
Zhou[197]	16	138 → 136	Decreased ambulatory BP	Patients at dry weight based on bioimpedance analysis and no change in postdialysis volume
Arramreddy[198]	13	140 → variable	NS	Variable Na individualized to predialysis plasma to achieve −2 mEq/L dialysate to plasma Na gradient
Manlucu[199]	16	137.8 → 135	Decreased	Biofeedback used to adjust dialysate Na

Abbreviations: BP, blood pressure; Na, sodium; NS, not specified.

sodium concentrations, confounding likely remains.[206-208] Taken together, it is the opinion of the Work Group that high dialysate sodium concentrations should be avoided, particularly among patients with consistently elevated BP or high interdialytic weight gain.

Research Recommendations

➢ Testing and validation of practical tools to ascertain dry weight

➢ RCTs determining the risk/benefit of altering dialysis sodium

➢ Randomized trials determining the effect of altering ultrafiltration rate on clinical outcomes

➢ Assessment of an ideal dietary sodium intake for dialysis patients

➢ Studies to further our understanding of both a minimum and an ideal treatment time while assessing clinical outcomes and patient preferences

Guideline 5: Hemodialysis Membranes

5.1 We recommend the use of biocompatible, either high or low flux hemodialysis membranes for intermittent hemodialysis. (1B)

RATIONALE

For this guideline, we reviewed 3 large RCTs that tested the hypotheses that high- versus low-flux dialyzers could improve either survival or CV outcomes in patients undergoing maintenance HD. The primary findings of each of these 3 trials showed no survival benefit, but a meta-analysis suggested that CV mortality was reduced in patients treated with high-flux membranes (HR, 0.82; 95% CI, 0.70-0.96).[209] Each of the 3 trials also showed statistically significant benefits of high-flux dialyzers on all-cause mortality for certain prespecified conditions (serum albumin ≤ 4 g/dL, undergoing maintenance HD for ≥ 3.7 years) or post hoc subgroups (patients with diabetes mellitus or AV fistulas). There were no differences between high- versus low-flux dialysis groups with respect to quality-of-life parameters. Importantly, none of the trials showed evidence for harm, including vascular access complications or infections. The committee considered this evidence in the context of cost. In a bundled environment, choosing a more costly therapy for all patients could reduce funds available for other potentially beneficial treatments. Given that the strength of evidence suggesting benefit is moderate, the committee decided to recommend that either high-flux dialyzers or low-flux dialyzers may be used, with each center weighing the potential CV mortality benefit with considerations such as local cost and availability. In regions with cost restraints, consideration may be given to utilization of high-flux dialyzers among those subgroups of patients suggested to have the most potential benefit.

While observational studies have suggested that high-flux dialyzers are associated with improved survival,[210-212] the primary findings of 3 large RCTs have failed to show a survival benefit with high- versus low-flux dialyzers.[129,213,214] The first trial was the HEMO Study, an RCT with a 2×2 factorial design. The HEMO Study included 1,846 prevalent patients, and one of the study comparisons evaluated the effect of high- versus low-flux membranes on the primary end point of all-cause mortality. For the primary end point, there was no significant effect of high- versus low-flux membranes on mortality. However, high flux was associated with a significant reduction in several secondary outcomes, including cardiac mortality and a composite outcome of cardiac hospitalization or cardiac death. In further post hoc analysis, an interaction between flux and years of dialysis was identified, in which patients treated with dialysis for more than 3.7 years prior to randomization had a lower risk of death with high- versus low-flux dialyzers, whereas there was no difference among those with fewer years of prior HD.

The second trial, the Membrane Permeability Outcome (MPO) trial, was a prospective randomized clinical trial inclusive of 738 incident HD patients randomized within stratum of serum albumin (>4 vs ≤ 4 g/dL) to high- versus low-flux dialyzers.[214] The primary analysis showed no significant difference in mortality with high- versus low-flux membranes. Based on an a priori subgroup analysis, there was a statistically significant reduction in all-cause mortality in the high-flux versus the low-flux group among participants with serum albumin ≤ 4 g/dL (relative risk [RR], 0.49 [95% CI, 0.28-0.87]). Post hoc subgroup analyses also demonstrated improved survival associated with high- versus low-flux dialyzers among those with diabetes.

The third trial was the EGE Study, which was a 2×2 factorial RCT inclusive of 704 patients comparing the effect of high- versus low-flux dialyzers on a combined outcome of fatal and nonfatal CV events.[213] There was no statistically significant difference in the primary outcome between high- and low-flux dialyzers (HR, 0.73; 95% CI, 0.49-1.08; $P = 0.1$). Post hoc analysis suggested a benefit associated with high- versus low-flux dialysis on improving CV event–free survival among those with AV fistulas and those with diabetes.

We reviewed one additional short-term randomized trial inclusive of 166 patients randomized to high- versus low-flux dialyzers with a 52-week end point of hemoglobin and ESA dose (Minoxis).[215] This trial reported no significant difference in all-cause mortality; CV mortality was not available. Inclusion of this trial did not affect the overall meta-analysis results demonstrating no significant effect of flux on mortality.

Regarding other important secondary outcomes, the effects of high-flux membranes on quality of life were assessed in the HEMO trial.[216] Participants responded to the Index of Well-Being and the Kidney Disease Quality of Life-Long Form questionnaires annually over 3 years. High-flux HD did not result in any change in health-related quality-of-life domains with the exceptions of sleep quality and patient satisfaction.

Importantly, there was no increased risk of harm with the use of high- versus low-flux dialyzers. There were no differences in the rate of hospitalizations for

infections or in vascular access problems between dialysis groups.

Taken together, the Work Group thought that high-flux dialyzers should be used preferentially. However, factors such as cost should be considered. In locations with cost restraints, patients with diabetes, lower serum albumin, or longer dialysis vintage should be considered a priority for selection of high-flux dialyzers.

Hemodiafiltration

The Work Group found 6 randomized trials comparing hemodiafiltration to either low-flux (3 trials)[217-219] or high-flux HD (3 trials).[220-222] Only 1 of the 6 trials (the Estudio de Supervivencia de Hemodiafiltración On-Line [ESOHL] trial of >900 patients) suggested significantly reduced all-cause and CV mortality with hemodiafiltration compared to high-flux HD.[13] These results are difficult to interpret given serious methodological limitations of this trial. In the original report, there are significant imbalances in baseline prognostic variables between the 2 groups, favoring the hemodiafiltration group (eg, younger age, lower diabetes prevalence, lower Charlson comorbidity score, and lower prevalence of catheters). In addition, a high proportion (39%) of patients discontinued

the study treatment and 20% of those randomized (excluding those who underwent transplantation) had no follow-up vital status information, precluding valid analysis of outcomes. In comparison, the CONTRAST (Convective Transport) Study[217] of over 700 patients lost only 12% of patients to follow-up and found no significant difference in patients treated with hemodiafiltration versus low-flux HD with respect to mortality or quality of life, despite adequate statistical power. The other 4 trials, while they had significant limitations, also found no benefit of hemodiafiltration. These findings are consistent with the results of 2 recently published meta-analyses of convective treatments compared to HD.[223,224] The Work Group recognized that this therapy is not widely available in the United States. Given the above evidence, we thought that further study is needed before hemodiafiltration can be recommended.

Research Recommendations

➢ Further understanding into the cost/benefit ratio of high- versus low-flux membranes
➢ Additional research is needed to understand whether there is a clinical benefit associated with hemodiafiltration versus conventional HD

Acknowledgements

Biographic and Disclosure Information

HEMODIALYSIS ADEQUACY: 2015 UPDATE WORK GROUP

John Daugirdas, MD (Chair), is a nephrologist and Clinical Professor of Medicine at the University of Illinois at Chicago. Dr Daugirdas has received the Chicago Top Doctor Award for multiple years. Research includes participation in 4 NIH/NIDDK-sponsored studies, the HEMO Trial, FHN trials, the TiMe Trial, and in the design of the Chronic Renal Insufficiency Cohort (CRIC) Trial. Dr Daugirdas is currently studying how much dialysis to prescribe using various schedules, as well as factors affecting blood volume and BP during HD. He also has a special interest in nutrition in CKD and phosphorus balance. Dr Daugirdas has a particular interest in medical education and is Co-Editor of the *Handbook of Dialysis* and Editor of the *Handbook of Chronic Kidney Disease Management*.

Financial Disclosure: Dr Daugirdas reports no relevant financial relationships.

Thomas Depner, MD (Chair), is an emeritus Professor of Medicine at the University of California, Davis, and the former medical director of the University Dialysis Clinic and Hemodialysis Services. He continues to engage in local and national committees that address HD. Dr Depner is currently a site principal investigator (PI) in NIH SPRINT (Systolic Blood Pressure Intervention Trial), a study of BP control in older people. His research interests focus on the prescription of HD and related issues, including the pathogenesis of uremia, identification of uremic toxins, and vascular access blood flow. Dr Depner received his MD from Johns Hopkins University School of Medicine and BS from University of Portland, Portland, OR.

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Financial Disclosure: Medical director salary from Quintiles and royalties from UpToDate.

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Financial Disclosure: Dr Rocco reports no relevant financial relationships.

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Financial Disclosure: Dr Suri holds an unrestricted Extramural Research Grant from Baxter Inc.

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investigating optimal BP targets in older adults with CV disease or CKD. Dr Weiner is the Deputy Editor of the *American Journal of Kidney Diseases* and the co-Editor in Chief of the National Kidney Foundation's Primer on Kidney Diseases, 6th edition. Dr Weiner is a member of the ASN's Public Policy Board and is the chair of the ASN Quality Metric Task Force. He has been a member of 2 dialysis Technical Expert Panels charged with developing metrics for the Centers for Medicare & Medicaid Services (CMS) to apply to dialysis care.

Financial Disclosure: Research and medical director funding from DCI.

KDOQI LEADERSHIP

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Financial Disclosure: Dr Kramer reports no relevant financial relationships.

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Financial Disclosure: Consultant funding from Galzxo Smith Kline, Data Monitoring Safety Board, and Genetech Advisory Board.

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Financial Disclosures: Dr Samaniego reports research grants and speakers bureau fees from Alexion Pharmaceuticals and consultant funding from Sanofi and Thermo-Fisher Corporation.

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Financial Disclosure: Dr Scheel reports no relevant financial relationships.

HEMODIALYSIS ADEQUACY: 2015 UPDATE EVIDENCE REVIEW TEAM

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