Update of the KDOQI™ Clinical Practice Guideline for Hemodialysis Adequacy

Running head: Hemodialysis Guideline Update

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DISCLAIMER

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon the best information available as of <<TBD>>. 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

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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 (i.e., 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 (e.g., 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

ABBREVIATIONS AND ACRONYMS

ABP	Arterial blood pressure
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
AV	Arteriovenous
BIA	Body impedance analysis
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CAPD	Continuous ambulatory peritoneal dialysis
CI	Confidence interval
C_i	Dialysate inlet conductivities
CKD	Chronic kidney disease
C_o	Dialysate outlet conductivities
CPR	Clinical Practice Recommendations
CV	Cardiovascular
D	Dialysance
DOPPS	Dialysis Outcomes and Practice Patterns Study
DRIP	Dry Weight Reduction Intervention
ECV	Extracellular volume
eGFR	Estimated glomerular filtration rate
ERT	Evidence Review Team
ESA	Erythropoiesis-stimulating agent
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	Kidney Disease Clinical Studies Initiative Hemodialysis
HR	Hazards ratio
IDEAL	Initiating Dialysis Early And Late
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Initiative
K_r	Residual kidney function
KRT	Kidney Replacement Therapy
LVH	Left ventricular hypertrophy
MDRD	Modification of Diet in Renal Disease
MPO	Membrane Permeability Outcome
Na	Sodium
NCDS	National Cooperative Dialysis Study
NIH	National Institutes of Health
NKF	National Kidney Foundation
NS	Not significant
PCR	Protein catabolic rate
PD	Peritoneal dialysis
PIDI	Preceding interdialysis interval
Q_b	Blood flow rate
Q_d	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
SCr	Serum creatinine
SCysC	Serum Cystatin C
SD	Standard deviation
sp	single-pool (Kt/V)
T	Treatment time in hours
Uf	Ultrafiltration rate
URR	Urea reduction ratio
USRDS	United States Renal Data System
V	Urea volume

EXECUTIVE SUMMARY

INTRODUCTION

When hemodialysis 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. Simplified standards however 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 continues to sponsor this forum for collaborative decision-making regarding the aspects of hemodialysis that are considered vital to achieve these goals.

Nearly 400,000 patients are currently treated with hemodialysis in the United States, with Medicare spending approaching $90,000 per patient per year of care in 2011[2]. Unfortunately, although mortality rates are improving, they remain several fold higher than that of age matched individuals in the general population, and patients experience an average of nearly two hospital admissions per year[2]. Interventions that can improve outcomes in dialysis are urgently needed. Attempts to improve outcomes have included initiating dialysis at higher glomerular filtration rates, increasing dialysis frequency and/or duration, using newer membranes, and employing supplemental or alternative hemofiltration.

Gathering the evidence

The literature reviewed for this adequacy update includes observational studies and clinical trials published from 2000 to 2013. 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 workgroup and evidence review team was to compile and evaluate as much information as possible to arrive at a reasonable answer to the questions posed in Table 1, not all of which can be answered definitively with support from controlled clinical trials.

Initiating hemodialysis

Despite lack of evidence from randomized controlled trials about the optimal time to start kidney replacement therapy, 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 comprise the best evidence regarding timing of dialysis initiation, motivating the update of this guideline[4].

Frequency and duration of dialysis

Observational and controlled non-randomized studies had suggested that more frequent and/or longer dialysis improves the patients quality of life, controls hyperphosphatemia, reduces hypertension, and results in regression of left ventricular hypertrophy[5,6]. Based on these findings, more frequent and longer dialysis sessions have become more common. Since the previous KDOQI update[7], several randomized controlled trials that compared more frequent or extended dialysis to conventional dialysis have been completed[8-11]. This update reviews this evidence.

Membranes and hemofiltration versus hemodialysis

Cardiovascular disease is the leading cause of death in patients with chronic kidney disease 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 cardiovascular outcomes. This update reviews the evidence for use of high flux compared to low flux dialyzer membranes as well as convective modes of kidney replacement therapy compared to conventional hemodialysis.

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 õbiocompatibleö 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 post-dialysis alkalosis, and dialysis-associated reductions in blood pressure, serum potassium, and serum phosphorus, and changes in other electrolytes and proteins that may amount to a õperfect stormö of stress potentially responsible for acute cardiac events as well as long term effects on the brain and cardiovascular system[12-14]. More frequent and more prolonged dialysis, while improving solute clearance and volume removal, could enhance blood-membrane interaction, add to 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 chronic kidney disease 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 patientøs dialysis started. Guidelines for some of these are addressed in other publications by the NKF/KDOQI including management of anemia, nutrition, metabolic bone disease, diabetes, and cardiovascular disease[18-22].

Structure of the workgroup

The volunteer members of the workgroup 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 kidney replacement therapy.

METHODS

In consultation with the NKF-KDOQI Hemodialysis Adequacy Clinical Practice Guidelines Update Work Group, the Minnesota Evidence Review Team (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 approach to the systematic literature review and the comprehensive findings prepared for this update are reported in detail elsewhere (Ref Evidence Report). 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 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 hemodialysis for CKD; to be included, studies needed to report the effects of an intervention on all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, all-cause hospitalization, quality of life, depression or cognitive performance, blood pressure or blood pressure 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 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 hemodialysis sessions, trials that assigned individuals to more frequent hemodialysis (>3 times a week) or longer (>4.5 hours) dialysis vs. conventional hemodialysis were included. For studies that compared high flux to low flux dialysis membranes, or hemofiltration or hemodiafiltration to conventional hemodialysis, the ERT included trials that enrolled at least 50 participants with a minimum of 12 months follow-up in each treatment arm.

Table 1. Questions posed at the start of the update initiative

In patients with chronic kidney disease, 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 inter-dialytic weight gains and high ultrafiltration rates have worse outcomes compared to patients with lower inter-dialytic weight gains and low ultrafiltration rates?
Do patients with extended (longer) or more frequent hemodialysis have greater blood pressure and volume control compared to 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 hemofiltration or 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 hemofiltration?

GUIDELINE STATEMENTS

The workgroup distilled these answers in the form of five guidelines, some of which are similar to the previous guidelines published in 2006[7] but have been re-emphasized or re-interpreted in light of new data. 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[23]: scales of A to D for quality of the evidence and 1 or 2 for the strength of the recommendation, including its potential clinical

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impact (Table 1). 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 where controversy exists but data are sparse, the guideline is ungraded, based on consensus opinion of the workgroup. For a few of the guidelines not all of the workgroup members agreed, and in such cases the reasons for disagreement are spelled out in the rationale that follows the guideline statement. For all of the guidelines, clinicians should be aware that circumstances may appear that would require straying from the recommendations of the workgroup.

Proposed Statements
Level 1 = Strong Recommendation
Level 2 = Conditional Recommendation/Suggestion
Grade A to D = evidence grade high to low
Ungraded = Not Graded

Grade for strength of recommendation

Grade*	Implications		
	Patients	**Clinicians**	**Policy**
Level 1 '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 a policy in most situations.
Level 2 '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 debate and involvement of stakeholders before policy can be determined.

* 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.

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.

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SUMMARY OF RECOMMENDATION STATEMENTS

Chapter 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. (ungraded)

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. (ungraded)

Chapter 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. (ungraded)

2.4 We recommend that patients considering frequently administered home long 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)

2.5 During pregnancy, women with end-stage kidney disease should receive frequent long hemodialysis either in-center or at home, depending on convenience. (ungraded)

Chapter 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 patient treated thrice weekly, with a minimum delivered spKt/V of 1.2. (1 B)

3.2 In patients with significant residual native kidney function (Kr), the dose of hemodialysis may be reduced provided Kr is measured periodically. (ungraded)

3.3 For hemodialysis schedules other than thrice weekly, 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. (ungraded)

Chapter 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 minimum of three hours per session. (1 D)

4.1.1 Consider longer hemodialysis treatment times or additional hemodialysis sessions for patients with large interdialytic 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). (Ungraded)

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. (1 B)

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. (Ungraded)

Chapter 5:
New Hemodialysis Membranes

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

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. (ungraded)

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. (ungraded)

RATIONALE FOR GUIDELINE 1.1

Recent KDIGO 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 kidney replacement therapy (KRT) to optimize decision making and outcomes.(1-3) While determining the rate of progression and precise timing of referral is beyond the scope of this guideline, the implication is clear ó that patients, their families, and caregivers should have ample time to make informed decisions regarding KRT and to implement these decisions successfully.(4)

Multiple dialysis modalities are available for KRT, none of which is conclusively demonstrated to be superior to the others.(5, 6) Additionally, conservative non-dialysis care may be the appropriate decision for many older or more infirm individuals,(7) while pre-emptive transplant may be the best for 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 caregivers are best positioned to determine which tradeoffs they are willing to make, particularly given lack of definitive evidence for the superiority of one dialysis modality over the other. Morton and colleagues recently provided a thematic synthesis of 18 qualitative studies that reported the experience of 375 patients and 87 caregivers.(8) They identified four 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). None of the essential decisions however can be made in an informed manner without adequate time for education and contemplation.

As illustrated by Morton and colleaguesø systematic review, electing conservative therapy rather than dialysis or kidney transplant is an important option for many people with kidney failure. In one study of 584 patients with CKD stages 4 and 5, 61% of the patients who had started hemodialysis regretted this decision (7), and when asked why they chose dialysis, 52% attributed this decision to their physician. While this study is limited by a homogenous population, it is apparent that education prior to dialysis regarding treatment options was insufficient in many, and 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.(9) 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 caregivers if possible, and to be continually reinforced in a positive and patient-sensitive manner.(4)

Given also the high prevalence of cognitive impairment (10) and delirium (11) among patients with kidney failure as well as acknowledged difficulties predicting the rate of progression to kidney failure among patients with advanced CKD (12-15), it is imperative that patientsø 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 (16, 17); accordingly, statements made on this topic are based on opinion and observational reports. In one US setting where pre-dialysis education was evaluated, individuals participating in an educational program were > 5 times more likely to initiate peritoneal dialysis and twice as likely to initiate hemodialysis with an arteriovenous 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 (18). However, even with timely education, many CKD patients may not initiate dialysis with their chosen modality; the reasons for this remain uncertain (19).

Studies over the last two decades have indicated that most patients starting maintenance dialysis in the United States are unaware of options for KRT other than in-center hemodialysis (20, 21). Despite the introduction of a Medicare benefit for CKD education over five years ago (22), many nephrology practices have not implemented structured education programs for stage 4 CKD patients and their families (23); 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 initiation of dialysis (24, 25).

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 hemodialysis is easiest to implement, peritoneal dialysis and conservative care are important options (4, 26-28). In the recent ¬Choosing Wiselyø 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 (29). In the opinion of the Work Group, this statement is appropriate for both planned and urgent dialysis initiations.

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 (30), better predictive instruments for determining when, if ever, an individual is likely to require KRT is 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 non-specific, 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 kidney replacement therapy 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 KRT initiation versus electing for conservative care becomes imperative.

While there is a need to estimate kidney function in patients with chronic kidney disease, and the level of kidney function should be considered when determining the timing of dialysis initiation, the Work Group felt 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 as well as 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 1A), the same association is not demonstrable with measured clearances (Table 1B) (31).

Currently, serum creatinine-based estimating equations are the most commonly used method to estimate GFR (Table 1C); 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 (32). Most commonly, in patients with advanced kidney disease, low muscle mass may result in over-estimation of GFR (Table 1D). To assist the decision making process and better align clinical symptoms with GFR, in selected cases direct measurement of GFR or of the clearance of 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 (32, 33). Ongoing investigations of existing and novel biomarkers may lead to improved estimations of GFR that can optimize the timing of dialysis initiation.

Accordingly, although favoring estimated GFR 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 chronic kidney disease, 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 does recognize the

potential utility of this in clinical situations where 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 (34). In this clinical trial conducted in 32 centers in Australia and New Zealand, 828 adult patients with creatinine clearance 10-15 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 subjects assigned to start dialysis early started later, and 76% of subjects assigned to start dialysis late started early. Hence, the mean creatinine clearance at the time of start of initiation of dialysis in the early and late groups was 12.0 and 9.8 ml/min/1.73 m^2 (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, cardiovascular or infectious events, or complications of dialysis. These results did not differ even when the analyses were restricted to individuals who started treatment with peritoneal dialysis.(35) Furthermore, the trend for higher total healthcare costs in individuals assigned to start dialysis early was not significantly different (36), and, in a sub-study, there was no difference in cardiac structure or function between earlier and later start groups.(37)

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 (38). 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 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 (4). Second, maintenance dialysis should not be denied to individuals with kidney failure who may potentially benefit from KRT, such as individuals with refractory volume overload or refractory hyperkalemia, simply because the GFR is considered õtoo highö.

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 (39). Uremia is a non-specific constellation of symptoms and signs superimposed on a low GFR (Table 1E); accordingly, these symptoms and signs, by definition, can have other causes. Providers need to be aware of uremia =mimickersø especially in the elderly and in 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 hemodialysis is similar (40). This raises the question, which if any of the symptoms commonly present in patients with kidney diseases would be expected to improve with KRT (41). Conversely, in many patients the decline in wellbeing is slow, without a discrete event that could be identified as the õappearance of uremic symptoms.ö 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 õartö of medicine.

Table 1A. 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

Author, Publication Year	Sample Size	Study Site	Study Period	Measure of Kidney Function	Hazards Ratio for association of kidney function at time of dialysis initiation with death risk
Fink, ‑99(42)	5,388	Veterans Affairs, Maryland, USA	04/95 to 12/96	Serum creatinine	For every 1 mg/dl higher serum creatinine: 0.96 (0.93, 0.99)
Traynor, ‑02(43)	235	Glasgow, UK	1987 - 2000	Cockcroft-Gault creatinine clearance	For every 1 ml/min higher creatinine clearance: 1.11 (1.01, 1.21)
Beddhu, ‑03(44)	2,920	Dialysis Morbidity and Mortality Study, USA	1996‑97	eGFR by MDRD equation	For every 5 ml/min higher eGFR: 1.14 (1.06-1.22)
Kazmi, ‑05(45)	302,287	United States Renal Data System	1996‑99	eGFR by MDRD equation	Death for risk for eGFR> 10 ml/min (Reference, < 5 ml/min): 1.42
Sawhney, ‑09(46)	7,299	Canada and Scotland	2000‑05	eGFR by MDRD equation	eGFR> 15 ml/min and 10-15 ml/min (Reference, 5-10 ml/min): 1.65 (1.39-1.95) and 1.37 (1.19-1.59) respectively
Stel, ‑09(47)	6,716	Europe	2003	eGFR by MDRD equation	For every 1 ml/min higher eGFR: 1.02 (1.01-1.04)
Evans, ‑11(48)	901	Sweden	05/ø96-05/ø98	eGFR by MDRD equation	eGFR > 7.5 ml/min (Reference: < 7.5 ml/min): 0.84 (0.64-1.10)
Hwang, ‑10(49)	23,551	Taiwan	07/ø10-12/ø04	eGFR by MDRD equation	Fifth quartile eGFR (> 6.52 ml/min) (Reference, first quartile, < 3.29 ml/min): 2.44 (2.11-2.81)
Lassalle, ‑10(50)	11,685	France	2002‑06	eGFR by MDRD equation	For every 5 ml/min increase: 1.09 (1.05, 1.14)
Wright, ‑10(51)	895,293	United States Renal Data System	01/95 ó 09/96	eGFR by MDRD equation	eGFR> 15 and 10-15 ml/min (Reference, 5-10 ml/min): 1.44 (1.43-1.45) and 1.15 (1.15-1.16) respectively
Grootendorst, ‑11(52)	569	Netherlands Cooperative Study n the Adequacy of Dialysis	1997-2005	eGFR by MDRD equation	Highest tertile of eGFR (Reference: lowest tertile): 1.4 (1.0, 1.9)
Rosansky, ‑11(53)	81,176	United States Renal Data System (non-diabetics, 45-64 yr old)	1995 to 2006	eGFR by MDRD equation	eGFR> 15.0 and 10.0 ó 14.9 ml/min (Reference, < 5 ml/min): 1.74 and 1.47 respectively
Crews, ‑14(54)	84,654, propensity matched 61,930	United States Renal Data System (×67 years old, ×2 years of prior Medicare coverage	2006 to 2008	eGFR by MDRD equation	eGFR ×10 ml/min per 1.73 m^2 (reference, <10 ml/min per 1.73 m^2): 1.11 (1.08 to 1.14) for propensity matched analyses
Crews, ‑14(55)	652 (187 initiating dialysis)	Cleveland Clinic	2005 to 2009	eGFR by MDRD equation	eGFR ×10 ml/min per 1.73 m^2 (reference, <10 ml/min per 1.73 m^2): OR, 0.85; 95% CI, 0.65-1.11 for inverse probability weighted analyses
Jain, ‑14(56)	8,047 initiating PD	Canadian Organ Replacement Register	2001 to 2009	eGFR by MDRD equation	eGFR >10.5 and 7.5-10.5 (reference, <7.5 mL/min/1.73 m2): adjusted HR, 1.08; 95% CI, 0.96-1.23) and adjusted HR, 0.96; 95% CI, 0.86-1.09, respectively

Table 1B. Summary data from observational studies that assessed the association between measured kidney function at the time of initiation of dialysis and risk for death

Author, Publication Year	Sample Size	Study Site	Study Period	Measure of Kidney Function	Hazards Ratio for association of kidney function at time of dialysis initiation with death risk
Bonomini, ʾ85(57)	340	Single Italian center		Creatinine clearance	12-year survival in early dialysis group, (mean creatinine clearance 12.9 ml/min), 77%; late dialysis group (mean creatinine clearance, 2.1 ml/min), 51%. No adjustment made for differences in patient characteristics
Tattersal, ʾ95(58)	63	Single UK center	1991-ʾ92	Renal Kt/V$_{urea}$	Mean renal Kt/Vurea lower in six individuals who died; no adjustment made for differences in patient characteristics
Churchill, ʾ97(59)	680	Canadian-USA Study on Adequacy of Peritoneal Dialysis (CANUSA)	9/90-12/92	24-hour mean of urinary urea and creatinine clearance	For every 5 L/week higher measured GFR: 0.95 (0.91, 0.99)
Beddhu, ʾ03(44)	1,072	Dialysis Morbidity and Mortality Study, USA	1996-ʾ97	Assumed 24-hour urinary creatinine clearance	For every 5 ml/min higher creatinine clearance: 0.98 (0.86-1.14)
Grootendorst, ʾ11(52)	569	Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)	1997-2005	24-hour mean of urinary urea and creatinine clearance	Highest tertile of measured GFR (Reference: lowest tertile of measured GFR): 1.0 (0.7, 1.3)

Table 1C. Commonly used validated GFR estimating equations in adults (From Levey, AJKD 2014) (32)

	MDRD Equation(60, 61)	CKD-EPI Equations		
Filtration Marker(s)	Serum Creatinine	Serum Creatinine (62)	Serum Cystatin C (63)	Serum Creatinine and Cystatin C (63)
Year Published	2006	2009	2012	2012
Coefficients				
Serum Creatinine	$SCr^{-1.154}$	---	---	---
Serum Creatinine, when >0.9 mg/dL for men or >0.7 mg/dL for women	---	$SCr^{-1.209}$ if male	---	$SCr^{-0.601}$
Serum Creatinine, when Ö0.9 mg/dL for men or Ö0.7 mg/dL for women	---	$SCr^{-0.329}$ if male $SCr^{-0.411}$ if female	---	$SCr^{-0.248}$ if male $SCr^{-0.247}$ if female
Serum Cystatin C, when >0.8 mg/dL	---	---	$SCysC^{-1.328}$	$SCysC^{-0.711}$
Serum Cystatin C, when Ö0.8 mg/dL	---	---	$SCysC^{-0.499}$	$SCysC^{-0.375}$
Age (per year)	$Age^{-0.203}$	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

MDRD, modification of diet in renal disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SCr, serum creatinine (in mg/dL); SCysC, serum cystatin C (in mg/dL).

For the MDRD Study, the coefficient of 21.154 for the exponent of SCr indicates that eGFR is 1.154% lower for each 1% higher SCr. For any value of SCr, older age and female sex are associated with lower eGFRcr, and African American race is associated with higher eGFRcr. For the CKD-EPI equations, creatinine is modeled as a 2-slope spline with sex-specific knots; SCysC is modeled as a 2-slope spline with the same knot for both sexes. The slopes are more steep above than below the knots. Because of the sex-specific knots for the creatinine coefficients, the sex coefficients in the CKD-EPI creatinine and creatinine. cystatin C equations are not comparable to MDRD Study and CKD-EPI cystatin C equations. The corresponding sex coefficients for the CKD-EPI creatinine and creatinine. cystatin C 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.

Table 1D. Clinical Settings Affecting Creatinine Generation (adapted from Stevens et al, NEJM 2006) (64)

Setting	Effect on Serum Creatinine
Demographic Characteristics	
Older age	Decreased
Female sex	Decreased
African AmericanÄ	Increased
HispanicÄ	Decreased
AsianÄ	Decreased
Clinical Characteristics	
Muscular habitus	Increased
Rhabdomyolysis	Increased
Loss of muscle (amputation, neuromuscular diseases, cachexia)	Decreased
Cirrhosis/advanced liver disease	Œ
Malnutrition/Inflammation	Decreased
Dietary Characteristics*	
Vegetarian/Vegan diet	Decreased
High meat diet	Increased

ÄRelative to white, non-Hispanic

ŒTubular secretion of creatinine in liver disease may also account for serum creatinine values that overestimate kidney function (65).

* Creatine supplements may artificially increase S.Cr (e.g. athletes)

Table 1E. Symptoms and Signs of UremiaÄ(adapted from Meyer and Hostetter, NEJM 2007) (39)

Symptoms	Signs
Fatigue	Seizures/Change in seizure threshold
Lethargy	Amenorrhea
Confusion	Reduced core body temperature
Anorexia	Malnutrition
Nausea	Insulin Resistance
Altered senses of smell and taste	Increased catabolism
Cramps	Serositis (pleuritis, pericarditis)
Restless legs	Hiccups
Sleep Disturbances	Platelet dysfunction
Pruritus	Somnolence

ÄWhile 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 table.

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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. (ungraded)

2.4 We recommend that patients considering frequently administered home long 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 frequent long hemodialysis either in-center or at home, depending on convenience. (ungraded)

BACKGROUND AND DEFINITIONS

Conventional hemodialysis remains the most common treatment for ESRD worldwide, and is usually performed for 3-5 hours, 3 days per week.[1-4] However, some dialysis programs now offer more õintensiveö hemodialysis regimens, characterized by either longer duration, increased frequency, or both. The Work Group for the KDIGO Controversies Conference on õNovel Techniques and Innovation in Blood Purificationö noted that there is no uniform nomenclature to describe the different types of intensive or more frequent hemodialysis.[5] Given the multitude of terms in the literature (e.g. daily, nocturnal, short-daily, daily-nocturnal, quotidian, frequent, intensive, etc.), it is often difficult to identify studies evaluating similar hemodialysis 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 hemodialysis regimens are compared and these variables are not considered. For these reasons, we believe that the nomenclature in the literature should be unified. <u>In concordance with the KDIGO Work Group[5], we suggest that all hemodialysis prescriptions specify the duration of the individual dialysis session, the number of treatments per week, blood and dialysate flow rates, the location for hemodialysis treatment, and the level of assistance</u>. A proposed nomenclature is summarized in Table 1.

Table 1. Descriptive Nomenclature for Various Hemodialysis Prescriptions

Proposed Name	Time of Day	Duration (hours per session)	Frequency (sessions per week)
Conventional HD	Daytime	3-5	3
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	Hemodialysis treatment in the patient's home		
Level of Assistance			
Fully assisted	Hemodialysis treatment is performed entirely by a health-care provider		
Partially assisted	The patient performs some (but not all) aspects of the hemodialysis treatment him or herself (eg. cannulation of fistula, connection/disconnection, setting machine, monitoring blood pressures, etc), while other aspects are performed by a health-care provider		
Self-care With unpaid caregiver Without unpaid caregiver	The patient performs all aspects of the hemodialysis treatment himself, 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		

[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.

EVIDENCE OVERVIEW

The 2006 guidelines did not contain graded guideline statements regarding frequent hemodialysis due to a paucity of evidence.[6,7] In one systematic review, Suri *et al* identified just 25 studies of short frequent hemodialysis (in-center or home) from 1990 to 2006 that included five or more adult patients with a follow-up period of at least three months, none of which were clinical trials, while Walsh, in a second systematic review, found 10 manuscripts and 4 abstracts

reporting on long frequent home hemodialysis with follow-up of 4 weeks or more, none of which were clinical trials. Short frequent hemodialysis improved blood pressure 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 hemodialysis improved blood pressure 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) hemodialysis was associated with high discontinuation rates (Suri). Both reviews highlighted serious methodological limitations of the then-existing literature on frequent hemodialysis, including small sample sizes, short follow-up time, non-ideal control groups, bias, and little information on potential risks.

The studies cited in the reviews by Suri and Walsh were the main evidentiary basis for the clinical practice recommendations in the 2006 hemodialysis guideline updates.[8] These recommendations suggested that more frequent hemodialysis may be of benefit to improve hyperphosphatemia, hypertension, chronic fluid overload, malnutrition, quality of life, quality of sleep, sleep apnea and/or sensitivity to erythropoiesis stimulating agents.

Since 2006, 3 parallel-arm randomized controlled trials of frequent hemodialysis have been completed: the Frequent hemodialysis Network (FHN) Daily (short frequent hemodialysis in-center) and Nocturnal (long frequent hemodialysis at home) Trials, and the Alberta nocturnal (long frequent hemodialysis at home) hemodialysis trial (Table 2).[9-11] The statements on frequent hemodialysis in the current guideline are mostly based on the results from these three 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 hemodialysis were also reviewed for this update.[12-16] Finally, we also included case reports and case series of outcomes during pregnancy with frequent hemodialysis, given the importance of this topic.[17,18]

Table 2. Summary: Randomized Trials of More Frequent Hemodialysis

Trial Name[9-11]	Hemodialysis Intervention	Frequency (days/week) (mean ± SD)	Time (hours/session) (mean ± SD)	Qb (ml/min) (mean ± SD)	Qd (ml/min) (mean ± SD)
FHN Daily[9]	Short frequent in-center	5.2 ± 1.1	2.57 ± 0.42	396 ± 42	747 ± 68
	Conventional HD	2.9 ± 0.4	3.55 ± 0.47	402 ± 41	710 ± 106
FHN Nocturnal[11]	Long frequent at home	5.1 ± 0.8	6.32 ± 1.03	262 ± 61	354 ± 106
	Conventional HD	2.9 ± 0.2	4.26 ± 1.08	350 ± 49	554 ± 126
Alberta Nocturnal[10]	Long frequent at home	5 to 6	⁻6 hours prescribed	m250 prescribed	~300 ml/min prescribed
	Conventional HD	3	Not reported	Not reported	Not reported

Qb= blood flow rate; Qd= dialysate flow rate

RATIONALE FOR GUIDELINES 2.1 AND 2.2

To date, just one randomized trial of short frequent hemodialysis has been completed.[9] The FHN Daily Trial randomized 245 patients to receive in-center frequent hemodialysis (1.5 to 2.75 hours, 6 days per week, minimum target eKt/Vn of 0.9 per treatment, where Vn = 3.271 x V2/3) or in-center conventional hemodialysis (minimum target eKt/V of 1.1, session length of 2.5 to 4 hours). Patients were followed for one 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 nine pre-specified secondary surrogate outcomes. The main study was not powered to examine mortality or other hard outcomes such as hospitalizations, although mortality data is available for extended follow-up participants after they completed their assigned interventions (see below).

Short-frequent hemodialysis resulted in statistically significant improvements in health-related quality of life and several surrogate outcomes. Patients receiving in-center short frequent hemodialysis 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 hemodialysis (mean difference 3.2, p=0.004).[9] In addition, in-center short frequent hemodialysis resulted in statistically significant reductions in left ventricular mass, intradialytic systolic blood pressure, antihypertensive medications, serum phosphorus, and use of phosphate binders. Mean differences in these variables (frequent minus conventional groups) were: -13.8 grams, 10.1 mm Hg, -0.64 medications per day, -0.46 mg/dL, and -1.35 equivalent phosphate binder doses per day). [9,32,33] On the other hand, there were no improvements in serum albumin levels (34) , cognitive function as measured by the Trailmaking test part B (35), depression as measured by the Beck Depression Inventory, mental health as measured by the mental health composite of the RAND (36), or objective measures of physical performance. (37) 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. (38)

The FHN Daily Trial also identified certain risks associated with frequent hemodialysis. Compared to patients receiving conventional hemodialysis, patients randomized to short frequent hemodialysis had a statistically significant increased risk of vascular access repairs (HR= 1.68, 95% CI 1.13 ó 2.51, p=0.01), primarily driven by increased vascular access repairs in the subgroup of patients with arteriovenous accesses at baseline.[19] All types of repairs appeared to be more prevalent with frequent compared to conventional hemodialysis, 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 hemodialysis on catheters was inconclusive as analysis of this subgroup lacked statistical power.

Other adverse outcomes were also examined. Compared to patients receiving conventional hemodialysis, more patients randomized to short frequent hemodialysis 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 hemodialysis had no effect on perceived caregiver burden.[20] The effects of short-frequent hemodialysis on residual kidney

function loss could not be examined, as patients entering the FHN Daily Trial were selected for minimal residual function at baseline. Finally, long-term adherence to the therapy was moderate, with 77.7% of patients receiving more than 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.[21] 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, ninety percent of patients randomized to daily hemodialysis reverted to 3 or 4 times per week hemodialysis. During the extended follow-up period of 2.7 years, using intention to treat analysis, there were 16 deaths in the daily hemodialysis arm and 25 deaths in the conventional arm. The overall relative hazard of mortality (short frequent versus 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 most 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 manuscript form.

Three retrospective observational studies evaluated the effect of in-center frequent hemodialysis on mortality.[12-14] Kjellstrand *et al* found significantly lowered mortality for European patients receiving in-center daily hemodialysis, but this analysis did not adjust for known confounders, including ESRD duration and comorbidities.[13] Moreover, the comparator group was from the United States, where HD mortality rates are known to be higher than for Europe.[22] In contrast, Marshall found no significant mortality difference between in-center frequent hemodialysis patients and appropriately matched controls, while Suri *et al* found patients receiving in-center short frequent hemodialysis were more likely to die.[12,14] Despite rigorous methodology, these two latter studies also have methodological limitations. Marshall 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 of the evidence, the effect of in-center short-frequent HD on survival remain uncertain.

In summary, because of the controversial and limited evidence regarding the effects of in-center short frequent hemodialysis 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 hemodialysis in the FHN Daily Trial was large.[23] In addition, the physiological benefits of short frequent hemodialysis demonstrated in the FHN Daily Trial were felt to be of considerable importance. The Work Group thus felt that patients should have the option to choose in-center short frequent hemodialysis over conventional hemodialysis 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 long-term adherence to 6 days per week therapy 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. These recommendations do not apply to short home hemodialysis therapies, or to dialysis prescriptions that are substantially dissimilar to the FHN Daily Study prescriptions.

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

RATIONALE FOR GUIDELINES 2.3 AND 2.4

Despite their popularity, there is no randomized trial evidence for the efficacy of in-center long hemodialysis therapies done 3 days or 3 nights per week or every other day or night dialysis. The Work Group thus decided not to make recommendations with respect to in-center long therapies.

The only randomized trial evidence that exists for long hemodialysis evaluated long frequent hemodialysis performed at home 5 to 6 nights per week compared to conventional home hemodialysis in the Alberta Trial and the FHN Nocturnal Trial.[10,11] (See Table 2 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).[10,11] Both trials demonstrated statistically better blood pressure and phosphate control with frequently administered home long hemodialysis, but no improvement in anemia.[32,33,38,39] 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 in 8% of participants in the Alberta study to prevent hypophosphatemia.[24] Left ventricular mass improved significantly in the Alberta Trial (mean difference of 15.3 grams, $p < 0.05$), with a non-significant improvement in the FHN Nocturnal Trial (mean difference of 10.9 grams, $p = 0.09$).[32,39] No effect on health-related quality of life measures were seen in either trial.[39]

Similarly, in the FHN Nocturnal Trial, there were no demonstrated improvement with long frequent hemodialysis in measures of cognitive function, depression, or nutrition, while in a subset of participants in the Alberta Trial, serum albumin levels improved in nocturnal subjects and declined in conventional HD subjects.[25, 34-36, 39]

Similar to short daily hemodialysis, risks were also identified in patients treated with long frequent hemodialysis in the FHN Nocturnal Trial.[19] 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 ó 5.59, p=0.07). Use of the buttonhole technique was associated with a longer period between successive arteriovenous access events compared to the rope-ladder technique (HR = 0.44; 95% CI, 0.20ó0.97; P=0.04), but infection events were too few to evaluate. Also of note

was a statistically and clinically accelerated loss of residual kidney function in the long frequent hemodialysis arm.[26] 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 two, was observed in patients treated with nocturnal compared to conventional dialysis.[26] Since residual kidney function is one of the most important favorable prognostic indicators in patients with end-stage kidney disease, this adverse effect of long frequent hemodialysis may have significant implications. Finally, compared to those randomized to conventional home hemodialysis, those randomized to long frequent hemodialysis experienced a trend to an increase in the burden they perceived on their unpaid caregivers; this was statistically significant after multiple imputation.[20] Finally, adherence rates were low to moderate with long frequent hemodialysis.

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 hemodialysis.[27] It is difficult to interpret these mortality data, given the high non-adherence rate with long frequent treatment, as well as the large percentage of crossovers in both arms after the main trial ended. Additional data on causes of death and hospitalization in this extended follow-up period have not yet been reported. A third randomized trial, the ACTIVE study, has recently reported results in abstract form (28). 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 ó 15 hours per week) dialysis and were followed for 12 months. The primary study outcome, quality of life, was similar in both groups at study end (mean difference in EQ5D 0.038 [95% confidence interval -0.03, 0.11] p=0.27). There was no difference in systolic blood pressure between groups, however, those subjects randomized to extended dialysis received fewer blood pressure lowering agents (mean difference -0.35 agents [-95% CI: 0.62, -0.08] p = 0.01).Randomization to extended hours was associated with a higher hemoglobin level and lower potassium and lower phosphate levels during followup (respective differences 3.51g/l [95% CI: 0.21, 6.81] p = 0.037; -0.28 mmol/l [95% CI: -0.43, -0.14] p = 0.0001; -0.17mmol/l [95% CI: -0.27, -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 two arms.

Two large observational studies suggested improved mortality with nocturnal hemodialysis, but these studies are inconclusive as they may be confounded by selection of healthier patients to undergo nocturnal hemodialysis therapy at home.[15,16] A 3rd study comparing home intensive (including short frequent, long thrice weekly, and long frequent hemodialysis) with home conventional hemodialysis found no difference in mortality.[14]

In the absence of further studies, 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 nocturnal hemodialysis 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 long frequent hemodialysis given the importance of vascular access and residual kidney function, and the caregiver burden identified in home hemodialysis patients.

Research Recommendations

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

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 hemodialysis 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. Note that this topic was not reviewed by the evidence review team and is thus based solely on the review and

interpretation of this literature by the workgroup.

Pregnancy in women with end-stage kidney disease is not common, but women who do conceive while undergoing conventional hemodialysis have very high rates of neonatal complications, including miscarriage, stillbirths, prematurity, and small for gestational age births.[29] Live birth rates with conventional hemodialysis (weekly dialysis time of 15 ó 24 hours for most reports) are estimated to be in the range of 50-87%.[29]

Several case-series have suggested that pregnancy-related outcomes might be improved with longer, more frequent hemodialysis treatments.[30,31] During a Canadian study of in-center long frequent hemodialysis, 22 pregnant women who received a weekly hemodialysis time of 48 ± 5 hours per week, at least 6 nights per week, carried their pregnancies to a mean of 36 weeks, with a 86% live birth rate and mean birth weight of 2118 ± 857 grams. 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 1748 ± 949 grams.[17] 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 Ö20 hours/week, 75% in women dialyzed for 30 hours per week, and 85% in women dialyzed for > 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 feel comfortable offering women with end-stage kidney disease less than 6 times per week therapy. They also recognized that strong evidence in the form of RCTs to definitively determine the effect of frequent vs. 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 felt that a strong recommendation should be made to use long frequent hemodialysis over conventional hemodialysis in pregnant women with end-stage kidney disease. However, the majority of members felt that the evidence base was too weak to support a recommendation, and thus an ungraded statement was made. While optimal session duration is not known, it should be noted

that in the Canadian cohort discussed above, live birth rates increased with increasing time per hemodialysis.[17]

Research Recommendations:

➤ To obtain better estimates of the risk of pregnancy-related complications with conventional HD vs. long frequent HD.

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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 patient treated thrice weekly, with a minimum delivered spKt/V of 1.2. (1 B)

3.2 In patients with significant residual native kidney function (Kr), the dose of hemodialysis may be reduced provided Kr is measured periodically. (ungraded)

3.3 For hemodialysis schedules other than thrice weekly, 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. (ungraded)

RATIONALE

Target dose (guideline 3.1)
Small solute clearance is currently considered the best measure of hemodialysis 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.

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 hemodialysis, 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 hemodialysis 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 non-representative. 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.

Evidence for the importance of urea clearance

For intermittent hemodialysis, 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 one controlled clinical trial have shown a strong correlation between urea Kt/V and mortality.[1,2,3] An additional clinical trial showed no survival benefit at higher levels of Kt/V[4] but previous studies clearly showed that lower values were strongly associated with increased morbidity and should therefore be avoided.[1,2]

Methods for measuring urea clearance

Urea Kt/V is most conveniently measured using mathematical modeling of the predialysis and postdialysis serum urea concentration.[5,6] This method provides an integrated or average clearance during the entire hemodialysis and is patient-specific, often called the õdelivered hemodialysis dose.ö

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 appendix #1), multi-compartment models, and on-line conductivity measurements (see appendix #5), not all of which generate the same value. An example of errors generated by simplified formulas is shown in Figure 1. Although the urea reduction ratio (URR) is easy to calculate and has been used as a standard to measure the delivered hemodialysis dose[8], 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 hemodialysis, and inability to incorporate the patient's residual kidney function in the expression of dose (see below).

A reference method against which other methods can be compared to guarantee uniformity and protect patients from under-dialysis is available on the Web (www.ureakinetics.org).[9] 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) ó see below, and surface area adjusted stdKt/V (SA-stdKt/V) (see appendix #4).

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 appendix #5). Conductivity clearances must be measured several times during each treatment to obtain an average for the entire hemodialysis. Methods for calculating Kt/V from conductivity measurements require a correction for cardiopulmonary recirculation[10,11] 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 (e.g., monitoring ultraviolet absorbance of spent dialysate) can only be used if equivalence to the reference standard noted above can be demonstrated.
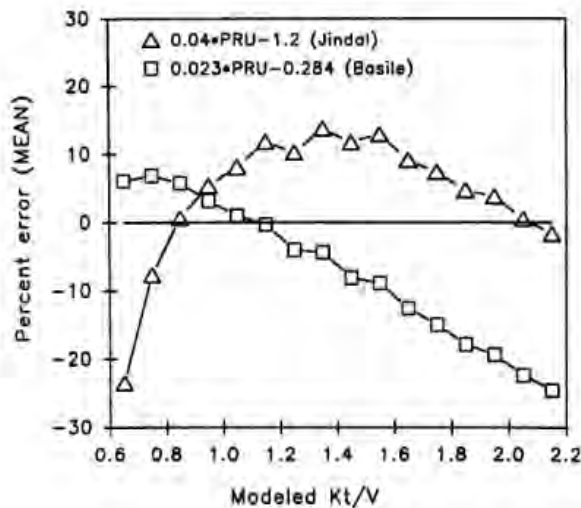

Figure 1. Systematic errors from two commonly used linear formulas based on PRU (percent reduction in urea concentration). The formula of Basile *et al*[12] has less error than the equation of Jindal *et al*[13] in the usual range but it overestimates the dose in the critical area of Kt/V<1.0.[14]

Kt/V calculated using the equilibrated postdialysis BUN (eKt/V) is recommended by some as a more accurate determinant of the dialysis effect.[15] Methods used to measure eKt/V require waiting 30 minutes after stopping hemodialysis 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 hemodialysis in patients with low residual native kidney clearance ((Kr) < 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.[7]

Adjustments for residual kidney function (Guideline 3.2)

Importance of Kr

The correlation between Kr and patient survival is strong and consistent among studies (see Figure 2).[16] Although a seemingly small contributor to urea clearance, a Kr value of 3 ml/min in the average patient is equivalent to a stdKt/V value of approximately 1.0 volume/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.[17,18] Loss of Kr has been postulated as a contributor to the increased mortality observed in patients dialyzed frequently at night.[19,20]
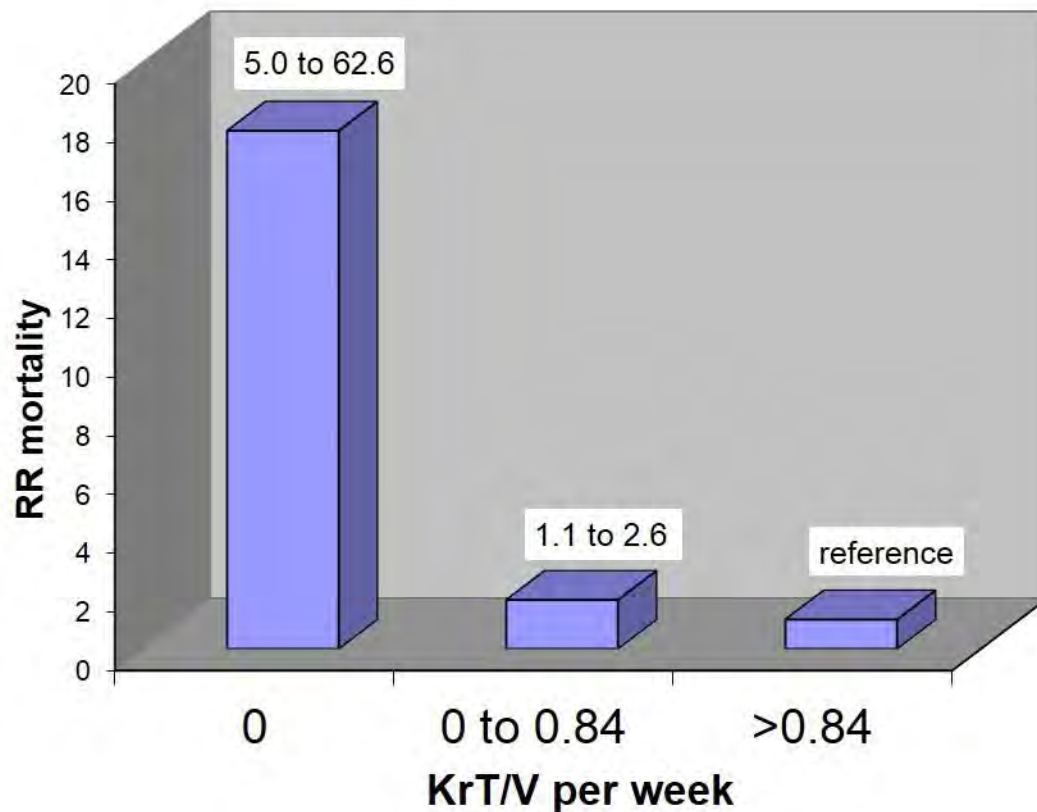

Figure 2. Data from the Netherlands Cooperative Study showing a marked increase in risk of death in patients with no residual native kidney function (KrT/V).[16]

Inclusion of Kr in the model of urea kinetics allows an accurate assessment of the urea generation rate from which the patientøs protein catabolic rate (PCR) can be determined. If the patient has significant Kr 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 compromise. However, if the targeted dialyzer Kt/V has been reduced because of significant Kr, and Kr 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 Kr is lost.

In such patients whose dialysis prescription has been modified by Kr, urine volume should be measured monthly.

Current methods for measuring Kr 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 appendix #2). To combine intermittent Kt/V with Kr, methods have been developed to account for the higher efficiency of continuous Kr compared to intermittent Kd (see appendix #4, and both the appendix (pp S75-77) and Clinical Practice Recommendations (CPR) for Guideline 2 in the previous KDOQI guidelines.[7]

Hemodialysis schedules other than thrice weekly (Guideline 3.3)
Standard Kt/V (stdKt/V) is the weekly urea generation rate factored by the average predialysis serum urea concentration during the week.[21,22] By definition, it includes the contributions of ultrafiltration during dialysis and residual kidney function.[23] StdKt/V was derived from attempts to account for the improved efficiency of more frequent and continuous dialysis treatments (as well as continuous Kr and PD) compared to less frequent intermittent hemodialysis, and is based on a comparison of achieved average solute concentrations in HD and PD patients. StdKt/V is considered a õcontinuous equivalent clearanceö 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.[24] A more detailed description of stdKt/V can be found in the previous KDOQI guidelines under CPRs 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 residual native kidney function (see appendix #3).

Since both spKt/V and stdKt/V are normalized by V, the patientøs 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 in the denominator, and are shown in appendix #4.[25]

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.[2,4] 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 hemodialysis, the patient is often left with symptoms and objective disorders that have been lumped together as a õresidual syndrome.ö[6,26] 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 patientøs kidney disease (e.g., diabetes mellitus, systemic lupus erythematosis, etc.) 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 hemodialysis.

APPENDIX

1. Method for estimating single pool Kt/V from the natural logarithm of the postdialysis/predialysis BUN ratio.

A linear equation has been developed and shown to give reliable results for spKt/V when applied to HD administered three times per week:[27]

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

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

$$spKt/V = -\ln(R \text{ ó } GFAC \times T) + (4 \text{ ó } 3.5 \times R) \times 0.55 \times \text{Weight loss}/V^{28}$$

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 Kr from serum samples at the beginning and end of the urine collection period.

   The serum urea concentration (BUN) fluctuates greatly during and between hemodialysis 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 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 a hemodialysis session to the beginning of the next. As a rough approximation the average of the pre- and post-BUN measured during the modeled hemodialysis session can be used in the calculation of Kr. Kr can be combined with the dialyzer urea clearance either by adding it directly to stdKt/V as shown below (appendix #3) or by inflating its value to account for the higher efficiency of continuous clearances, and then adding it to spKt/V as outlined in the appendix to the previous KDOQI guidelines (Table 18).[7]

3. Method for estimating stdKtV from spKt/V

   Standard Kt/V (stdKt/V) was conceived by Gotch 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).[22] The calculation was based on a fixed volume model of urea kinetics during an entire week. The original method was later simplified by Leypoldt[29] and then further enhanced by Daugirdas who included the patient's ultrafiltration rate (Uf) and residual kidney function (Kr).[23] As originally defined by Gotch[22], stdKt/V includes the effects of Uf and Kr. However, when measured using modeled values for G, eKt/V, and avCpre, the contribution of Kr is inappropriately downgraded because G/avCpre assumes that the Kr component also uses the average predialysis BUN instead of the average BUN in the denominator. To correct for this error when Kr is included, modeled values for G and V must be used to calculate stdKt/V in the absence of Kr which can then be added as Kr x 10080/V.[23]

The following set of equations allow a reasonable approximation of true stdKt/V from spKt/V with accurate contributions by Uf and Kr:[22,23,29]

$$eKt/V = spKt/V \ (t/(t + 30))^{30}$$

$$_{std}Kt/V = \frac{10080\frac{1-e^{-eKt/V}}{t}}{\frac{1-e^{-eKt/V}}{eKt/V}+\frac{10080}{Nt}-1} \qquad \text{(fixed volume model, no Kr)}$$

$$\text{std}Kt/V \;=\; \cfrac{S}{1 - \cfrac{0.74}{F}\left[\dfrac{U_f}{V}\right]} \;+\; K_r\dfrac{10080}{V} \qquad\qquad \text{(variable volume model with } K_r\text{)}$$

S is   stdKt/V derived from a fixed volume model
(2nd 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.

K_r is the residual native kidney clearance of urea in ml/min.

10080 is the number of minutes in a week.

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

To protect patients from under-dialysis, the contribution of K_r should be added only if a measurement has been done within three months prior to the modeling date.

4. Method for calculating SA-stdKt/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 post-dialysis 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 body surface area (BSA). A secondary analysis of the HEMO data, which showed improved outcomes in women but not in men treated at the higher hemodialysis dose, raised concerns about possible inappropriate use of V as the dose denominator in women and smaller patients (see Figure 3 below).[25,31] 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:[23,32,33]

$$\text{SA}_\text{std}Kt/V = \frac{\text{std}Kt/V}{20} \bullet \frac{V_W}{BSA}$$

SAstdKt/V is the surface area-normalized standard Kt/V (fraction/week).

V_W is the patient's volume of urea distribution determined by the Watson formula (liters).[34]

BSA is the patient's surface area based on height and weight (m^2).[35]

20 is a normalizing factor (the mean V/BSA, L/m^2).

Figure 3. (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.[4,25]
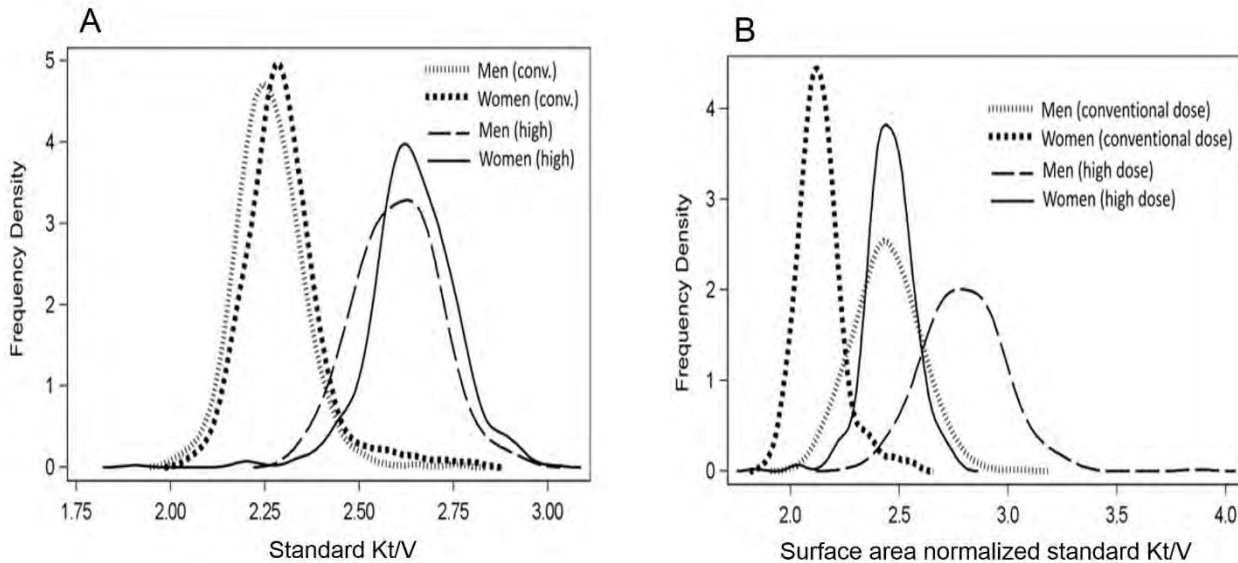
5. Method and equations for measuring conductivity dialysance.

$$D = [Qd + Qf][1 – (Co_1 – Co_2)/(Ci_1 – Ci_2)]^{36}$$

Co & Ci are dialysate outlet and inlet conductivities (mS/cm)
D is dialysance (ml/min)
Qd is dialysate flow
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.[11,36]

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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 minimum of three hours per session. (1 D)

    4.1.1 Consider longer hemodialysis treatment times or additional hemodialysis sessions 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). (Ungraded)

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. (1 B)

    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. (Ungraded)

RATIONALE FOR GUIDELINE 4.1

The optimal duration of each hemodialysis (HD) session for patients treated thrice weekly remains unknown. In the National Cooperative Dialysis Study, the difference in hospitalizations rates for patients assigned to different treatment durations did not reach statistical significance (p=0.06) (1). Similarly, in the HEMO study, a randomized controlled clinical trial (RCT) evaluating different targets for small molecule clearance in patients undergoing in-center, conventional hemodialysis, 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 (2). In the FHN Nocturnal trial, which randomized 87 patients to more frequent treatment and longer treatment times or conventional home hemodialysis, more frequent and longer dialysis treatment was not associated with any significant change in left ventricular mass (3). In contrast, the Canadian nocturnal HD trial(4) demonstrated significant regression of left ventricular hypertrophy with nocturnal HD (4). In an older randomized cross-over study of 38 patients treated for two weeks with 5 vs 4 hours of dialysis, five hours of hemodialysis was associated with greater hemodynamic stability and fewer hypotensive episodes, especially among patients > 65 years old (5), 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 trial (clinicaltrials.gov NCT02019225), an ongoing 3-year pragmatic RCT comparing longer HD treatments (4.25 hours) with conventional HD prescriptions in incident hemodialysis 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 hemodialysis sessions with higher mortality (6-8). 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 (hazard ratio)=0.75, (95% confidence interval=0.61-0.91), P=0.004]. Additionally, nocturnal hemodialysis was associated with lower blood pressure, 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 (9). 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 blood pressure (10). Conversely, longer HD sessions appear associated with better control of blood pressure, possibly due to achieving better extracellular volume (ECV) control (11, 12). Control of ECV with the combination of dietary sodium restriction and appropriate ultrafiltration with (13) or without (14, 15) 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 hemodialysis (4-5 hours) (16). 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 (17).

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 residual kidney function (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 õbare minimum.ö 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 hemodialysis, blood pressure control, overall metabolic control (including ability to manage metabolic acidosis, serum phosphorus and potassium, for example),

residual kidney function, patient preference, and health-related quality of life also be considered when making a decision regarding hemodialysis treatment time. Longer treatment times may be required for patients with high inter-dialytic weight gain, high ultrafiltration rates, poorly controlled blood pressure, difficulty achieving dry weight, or poor metabolic control.

RATIONALE FOR GUIDELINE 4.2

Although hypertension affects 60-90% of hemodialysis 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 cardiovascular events in patients undergoing maintenance hemodialysis with higher pre-dialysis blood pressures. In contrast, observational data suggest higher risk of death in patients with low systolic blood pressure, both pre- and post-hemodialysis (18). 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 blood pressure in these observational studies likely reflects confounding from comorbid conditions like cardiovascular disease and protein-energy wasting. In at least one prospective study, higher mean arterial blood pressure was associated with the development of progressive concentric left ventricular hypertrophy, *de novo* ischemic heart disease, and *de novo* congestive heart failure (19). It is the opinion of the Work Group that control of blood pressure is likely important to reduce the high cardiovascular risk of patients undergoing maintenance dialysis. While the ongoing Blood Pressure in Dialysis trial may provide further information about the effects of different blood pressure targets in hemodialysis patients on cardiac morphology (20), the current paucity of clinical trial data does not allow defining the target pre-dialysis, post-dialysis, or ambulatory blood pressure for HD patients.

The prevalence and severity of hypertension in patients undergoing maintenance hemodialysis is in part attributable to sodium and water retention and extracellular volume expansion (21-23). No RCTs have tested the hypothesis that one method of blood pressure control is superior to another in improving outcomes, but, considering that ECV expansion is an important contributor to elevated blood pressure, it is the opinion of the Work Group that reducing extracellular volume should be the first line of treatment. Achievement of true dry weight, which still remains a largely clinical determination, is necessary for control of blood pressure (21, 24-26), while failure to achieve target dry weight associates with higher all-cause and cardiovascular mortality (27, 28). In one small clinical trial, targeted reduction in extracellular volume using bio-impedance guidance improved blood pressure, left ventricular hypertrophy and arterial stiffness when compared to usual care assessment of dry weight and determination of ultrafiltration rate (29). However, the effect of controlling BP and reducing LVH on patient-centered outcomes such as hospitalization, cardiovascular 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 hemodialysis. The Dry Weight Reduction Intervention (DRIP) trial is the largest RCT demonstrating the effect of dry weight reduction on BP control (30). In this study, 150 hemodialysis 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 mmHg greater reduction in ambulatory BP at 8 weeks (30). 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 hemodialysis procedure is dictated, in part, by the ultrafiltration rate, which in turn is determined by the inter-dialytic weight gain and length of each session. No RCTs have tested the hypothesis that reducing inter-dialytic weight gains or reducing ultrafiltration rates can improve patient-centered outcomes. Observational studies suggest that both large inter-dialytic weight gain and high ultrafiltration rate are associated with higher mortality (31-35). 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 inter-dialytic weight gain (> 4.8% of body weight, > 5.7% of body weight, $\times$ 4.0 kg, and $\times$ 3 kg respectively) were associated with adverse outcomes. It should be highlighted that the overall goals of reducing inter-dialytic weight gain are to try to maximize tolerability of hemodialysis and to avoid chronic extracellular volume overload, which is associated with higher CV morbidity and mortality (36).

Higher ultrafiltration volumes have been shown to be associated with higher odds of myocardial stunning (37). In addition, hemodialysis itself is associated with decreases in myocardial blood flow that are accentuated by ultrafiltration (38). These data suggest that microcirculatory changes are not solely due to reductions in plasma volume and may be caused by other factors as well (39). 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 hemodialysis procedure.

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 hemodialysis 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 (40). 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 hemodialysis 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 1). Most of these small studies demonstrated that lowering dialysate sodium is associated with reduced BP burden.

Table 1. Published clinical studies on the effect of lowering dialysate sodium on subsequent blood pressure.

Reference	N	Dialysate Na Change (mEq/L)	BP effect	Comments
Krautzig (13)	8	140 → 135	Decreased	Also dietary Na restriction and fixed Na decrease
Farmer (42)	10	138-140 → 133-135	Decreased	Fixed decrease in Na, ABP measured
Kooman (43)	6	140 → 136	NS	Fixed decrease in Na
Ferraboli (44)	14	140→135	Decreased	Fixed decrease in Na
De Paula (45)	27	138→135	Decreased	Tailored decrease in Na
Lambie (46)	16	136→variable	Decreased	Progressive titration in Na based on dialysate conductivity
Sayarlioglu (47)	18	Variable based on preHD Na	Decreased	Decreased IVC diameter
Zhou (48)	16	138→136	Decreased ABP	Patients at dry weight based on BIA and no change in postdialysis volume
Arramreddy (49)	13	140→variable	NS	Variable Na individualized to predialysis plasma to achieve . 2 mEq/L dialysate to plasma Na gradient
Manlucu (41)	16	137.8→135	Decreased	Biofeedback used to adjust dialysate Na

As mentioned above, sodium loading during hemodialysis clearly results in greater thirst with resultant volume expansion, increased cardiac workload and subsequent hypertension. Interestingly, recent *in vitro* studies suggest exposure to high sodium may result in hypertension independent of its effects on extracellular volume. 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 (50-54).

In summary, high sodium diet, volume expansion, and exposure to high sodium dialysate all result in high blood pressure in hemodialysis 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 (55). While observational studies do not suggest benefit associated with lower dialysate sodium concentrations, confounding likely remains (56-58). Taken together, it is the opinion of the Work Group that high dialysate sodium concentrations should be avoided, particularly among patients with consistently elevated blood pressure or high inter-dialytic weight gain.

Research Recommendations:
- ➢ Testing and validation of practical tools to ascertain dry weight
- ➢ Randomized controlled trials 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

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Guideline 5
Hemodialysis Membranes

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

RATIONALE

For this guideline, we reviewed 3 large randomized controlled trials that tested the hypotheses that high vs low flux dialyzers could improve either survival or cardiovascular outcomes in patients undergoing maintenance hemodialysis. The primary findings of each of these 3 trials showed no survival benefit, but a meta-analysis suggested that cardiovascular mortality was reduced in patients treated with high-flux membranes (HR 0.82, CI 0.70-0.96).[1] Each of the 3 trials also showed statistically significant benefits of high-flux dialyzers on all-cause mortality for certain pre-specified conditions (serum albumin Ö4 g/dL, years, undergoing maintenance hemodialysis for × 3.7 years) or *post-hoc* subgroups (patients with diabetes mellitus or arteriovenous fistulae). There were no differences between high vs. 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 high flux dialyzers be used preferentially over low flux dialyzers, but that considerations such as local cost and availability be considered. 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,[2-4] the primary findings of 3 large randomized controlled trials have failed to show a survival benefit with high vs low flux dialyzers.[5-7] The first trial was the HEMO study, a randomized controlled trial with a 2x2 factorial design. The HEMO study included 1846 prevalent patients, and one of the study comparisons evaluated the effect of high versus low flux membranes on the primary endpoint of all-cause mortality. For the primary endpoint, there was no significant effect of high vs 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, where patients treated with dialysis for more than 3.7 years prior to randomization had a lower risk of death with high vs low flux dialyzers, whereas there was no difference among those with fewer years of prior hemodialysis.

The second trial, the Membrane Permeability Outcome (MPO) trial, was a prospective randomized clinical trial inclusive of 738 incident hemodialysis patients randomized within stratum of serum albumin ($>$ vs $\leq$ 4 g/dl) to high vs low flux dialyzers.[6] The primary analysis showed no significant difference in mortality with high vs 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 a serum albumin Ö4 g/dl (RR 0.49 [95% CI 0.28 to 0.87]). *Post-hoc* subgroup analyses also demonstrated improved survival associated with high vs low flux dialyzers among those with diabetes.

The third trial was the EGE study, which was a 2x2 factorial randomized controlled trial inclusive of 704 patients comparing the effect of high vs low flux dialyzers on a combined outcome of fatal and nonfatal cardiovascular events.[7] There was no statistically significant difference in the primary outcome between high and low-flux dialyzers (HR 0.73, CI 0.49-1.08, p =0.1). *Post-hoc* analysis suggested a benefit associated with high vs low flux dialysis on improving CV event free survival among those with arteriovenous fistulas and those with diabetes.

We reviewed one additional short-term randomized trial inclusive of 166 patients randomized to high vs low flux dialyzers with a 52 week endpoint of hemoglobin and ESA dose (Minoxis).[8] This trial reported no significant difference in all-cause mortality; CV mortality was not available. Inclusion of this trial did not impact 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.[9] Participants responded to the Index of Well-Being and the Kidney Disease Quality of Life-Long Form questionnaires annually over three years. High-flux hemodialysis 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 vs 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 felt 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) [10-12] or high flux hemodialysis (3 trials).[13-15] Only one of the 6 trials (the ESOHL trial of over 900 patients) suggested significantly reduced all-cause and cardiovascular mortality with hemodiafiltration compared to high-flux hemodialysis.[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 (for example, lower 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 were transplanted) had no follow-up vital status information, precluding valid analysis of outcomes. In comparison, the CONTRAST study[10] 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 hemodialysis 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 two recently published meta-analyses of convective treatments compared to hemodialysis.[16,17] The Work Group recognized that this therapy is not widely available in the US. Given the above evidence we felt that further study is needed before hemodiafiltration can be recommended.

Research Recommendations:

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

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EGE study group

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