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Executive Summary of the Korean Society of Nephrology 2021 Clinical Practice Guideline for Optimal Hemodialysis Treatment

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The Korean Society of Nephrology (KSN) has published a clinical practice guideline (CPG) document for maintenance hemodialysis (HD). The document, 2021 Clinical Practice Guideline on Optimal HD Treatment, is based on an extensive evidence-oriented review of the benefits of preparation, initiation, and maintenance therapy for HD, with the participation of representative experts from the KSN under the methodologists' support for guideline development. It was intended to help clinicians participating in HD treatment make safer and more effective clinical decisions by providing user-friendly guidelines. We hope that this CPG will be meaningful as a recommendation in practice, but not on a regulatory rule basis, as different approaches and treatments may be used by health care providers depending on the individual patient's condition. This CPG consists of eight sections and 15 key questions. Each begins with statements that are graded by the strength of recommendations and quality of the evidence. Each statement is followed by a summary of the evidence supporting the recommendations. There is also a link to full-text documents and lists of the most important reports so that the readers can read further (most of this is available online).

Keywords: Evidence-based practice, GRADE approach, Hemodialysis units, Hospital, Practice guideline

Introduction

Over the past 60 years, due to the advancement of hemodialysis (HD) technology and the introduction of medical insurance, dialysis treatment has become widespread, enabling many patients with end-stage kidney disease (ESKD) to maintain their lives. The treatment of dialysis patients has also evolved considerably. Depending on the circumstances, various clinical practice guidelines (CPGs) for initiating and maintaining HD have been published internationally. However, the clinical field, the technology of HD, and the target patients covered in previously published CPGs are subject to change. In addition, because the clinical evidence for HD has been reinforced in follow-up studies after

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the publication of previous CPGs, there is now a demand for reevaluation of these CPGs in accordance with current conditions. In response, the Korean Society of Nephrology (KSN) established the Work Group and tasked it with planning, developing, reviewing, and disseminating appropriate HD treatment guidelines in accordance with international standards. The level of evidence was evaluated using the Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology. The importance of each result is evaluated first, and then the level of evidence for each result is determined as high, moderate, low, or very low. The meaning of each evidence level is shown in Table 1. The recommendation grade was divided into four levels: strong, conditional, against, and inconclusive (Table 2). Key questions that cannot be adapted and developed directly due to poor existing research are expressed as "expert consensus."

Chapter 1. Start of hemodialysis

Recommendation 1.1

We recommend that whether and when to start HD be decided through a careful discussion between the patient and the healthcare provider about the benefits/harms of the treatment and the patient's values and preferences about HD initiation because an early start of HD, as determined by the glomerular filtration rate (GFR), in patients with chronic kidney disease (CKD) stage G5 does not produce any differences in clinical outcomes from a late start.

(Strong recommendation, moderate quality of evidence)

When to begin dialysis is influenced by a variety of factors, including signs and symptoms of uremia, biochemical tests, and the patient's GFR. As the precise timing will likely affect the cost of dialysis services and clinical outcomes, certain factors related to mortality, degree of improvement in symptoms and functions, quality of life, and other medical expenses should be considered.

No published studies have investigated the timing of the initiation of dialysis based on patient symptoms. One randomized study (IDEAL; Initiating Dialysis Early and Late) compared the clinical outcomes of relatively early- and late-starting groups based on GFRs [1], and three subanalyses of this randomized study have been reported [2–4]. Only a comparison between the early-start group and the late-start group based on GFR was available; early (10–14 mL/min/1.73 m^2) and late (5–7 mL/min/1.73 m^2)

Table 1. GRADE quality levels of evidence and meaning

Quality level	Definition
High	We are confident that the estimate of the effect is close to the actual effect.
Moderate	The estimates of the effect appear to be close to the actual effect, but it can vary considerably.
Low	The confidence in the estimate of the effect is limited. The actual effect could differ significantly from the estimate of the effect.
Very low	There is little confidence in the estimate of the effect. The actual effect will differ significantly from the estimate of the effect.

GRADE, Grading of Recommendations Assessment Development and Evaluation.

Table 2. GRADE strength of recommendation and meaning

Strength	Definition
Strong recommendation (We recommend)	Considering the benefits and risks of the treatment, the level of evidence, patient values and preferences, and resources, it is strongly recommended in most clinical situations.
Conditional recommendation (We suggest)	The use of the treatment can vary depending on the clinical situation or patient/social values, so it is recommended for use selectively or conditionally.
Against recommendation (We recommend not)	The risk of the treatment could outweigh the benefit, so taking into account the clinical situation and patient/social values, implementation is not recommended.
Inconclusive (Data are insufficient)	Considering the benefits and harms of the treatment, patient values and preferences, and resources, the level of evidence is too low, the scale of benefits/hazards is seriously uncertain, or the variability is so large that no decision to implement the intervention can reasonably be made. In the absence of a recommendation or objection to the use of the treatment, clinicians must follow their own judgment.
Expert consensus (We consider it reasonable)	Although clinical evidence is insufficient, the treatment is recommended for use in accordance with clinical experience and expert consensus, in consideration of the benefits and risks of the treatment, the level of evidence, patient values and preferences, and resources.

GRADE, Grading of Recommendations Assessment Development and Evaluation.
Each statement is shown as a combination of the strength of the recommendation and level of evidence.
In the case of a consensus statement based on expert opinion, the recommendation grade and level of evidence are not indicated.

start times were defined. The analysis found no significant difference between the two groups in major clinical outcomes, such as mortality, quality of life, hospitalization, and infection [1].

In addition, based on various retrospective studies, including domestic research, we synthesized evidence in a meta-analysis [5–14]. After classifying retrospective studies according to design and similarity of selected groups, no benefit or harm was apparent for the relatively early-start patients compared to the late-start group. However, because the heterogeneity between the retrospective studies used in the synthesis of evidence was high, and there was no consistency in the quality evaluation, all were evaluated at a moderate level of evidence.

Recommendation 1.2

1. We recommend the preparation of an arteriovenous access prior to HD initiation to avoid central venous catheter insertion. (Strong recommendation, low quality of evidence)
2. We consider it reasonable that the timing of an arteriovenous access preparation be individualized according to patient comorbidities and GFR decline. (Expert consensus)

The purpose of preparing arteriovenous access for HD using an arteriovenous fistula (AVF) or arteriovenous graft (AVG) is to avoid unnecessary central venous catheter insertion at the timing of dialysis initiation. Central venous catheter insertion may be associated with catheter-related infection, central vein stenosis, pneumothorax, and additional medical expenses, which are typically unnecessary.

Most studies of the preparation of arteriovenous access investigated clinical outcomes by types of arteriovenous access and timing of preparation. No randomized controlled trials have been reported, and most research was observational in nature and based on cohort data. Low mortality and low hospitalization rates were reported in native AVF groups [15–18], but selection bias cannot be excluded due to the nature of the observational studies.

Although survival benefits of patients with a native AVF had been reported in some studies, it has also been associated with maturation failure [17]. Preparation of AVF and AVG has been described as a trade-off for elderly patients. The use of AVGs was superior with respect to maturation, leading to reduced duration of central venous catheter placement and less intervention for delayed vascular access maturation. However, AVG was accompanied by more vascular access abandonment and secondary operation after maturation. Compared to AVG, AVF involved longer vascular access survival and less secondary intervention after maturation.

Although there is no direct evidence regarding the optimal timing of referral of arteriovenous access preparation, the recent Kidney Disease Outcomes Quality Initiative (KDOQI) stated that referral for dialysis access assessment and subsequent creation should occur when the GFR is 15–20 mL/min/1.73 m^2, based on expert opinion. They also stated that earlier referral should occur in patients with unstable and/or rapid rates of GFR decline (>10 mL/min/year) [19], based on a well-designed Monte Carlo simulation model [20].

Chapter 2. Frequency and dose of hemodialysis

Recommendation 2.1

We recommend maintaining a dialysis at a frequency of at least three sessions per week and for 4 hours or more for patients with minimal residual renal function. (Strong recommendation, moderate quality of evidence)

Since Scribner introduced intermittent maintenance HD in patients with ESKD in 1960, a typical HD schedule has been three sessions for 10–12 hours per week. In Korea, the frequency of dialysis is three sessions a week, for 12 hours. Various frequencies of HD treatments, such as daily home HD sessions, are not mentioned in this guideline due to medical insurance issues in Korea. It is difficult to define the appropriate number and duration of dialysis sessions separately. We therefore examined and summarized related studies about relevant sessions and the time of dialysis.

In two randomized controlled studies of HD patients who received dialysis three times a week, no significant differences in mortality (odds ratio [OR], 1.02; 95% confidence interval [CI], 0.88–1.18; p = 0.79) and hospitalization rates (OR, 1.38; 95% CI, 0.67–2.87; p = 0.38) were reported between the two groups (patients receiving more than 4 hours and less than 4 hours of HD per session) [21,22]. However, in the four cohort studies in which a meta-analysis was possible, the mortality rate (OR, 1.34; 95% CI, 1.15–

1.55; p < 0.01) was higher in the group receiving less than 4 hours of dialysis compared to the group receiving more than 4 hours [23–26]. Based on these findings, the dialysis frequency in patients with minimal residual renal function should be at least three times a week, with sessions lasting at least 4 hours [27]. Charra et al. [28] reported improved blood pressure control through long HD (3 × 8 hours/week). Marshall et al. [29] found that the mortality rate was lower among patients receiving more than 4.5 hours of HD per session.

In addition, studies show that it is possible to try initiating twice-weekly HD in patients who retain significant residual kidney function. A meta-analysis of three studies found that the mortality rate tended to increase in HD patients without residual renal function, suggesting it should only be attempted while monitoring carefully for changes in residual renal function [30– 32].

Recommendation 2.2
We recommend a target dose of 1.4 single-pool Kt/V (spKt/V) for patients receiving thrice-weekly HD.
(Strong recommendation, moderate quality of evidence)

The adequacy of HD has been traditionally measured by evaluating the clearance of small molecules such as urea. Since the advent of the Kt/V measure, which consists of dialyzer clearance (K), dialysis time (t), and volume of distribution (V), many observational studies have consistently reported that dialysis with an increased Kt/V was significantly associated with survival benefits in patients on HD [25,33–42].

The representative study for this issue is the HEMO (Hemodialysis) Study published in 2002 [43]. In this randomized clinical trial involving 1,846 patients undergoing thrice-weekly HD, the high-dose group maintaining a mean spKt/V of 1.71 enjoyed no significant benefit of morbidity and mortality compared to the standard group maintaining a mean spKt/V of 1.32.

Because the aforementioned observational studies reported that increased mortality was associated with an inadequate dialysis dose, maintaining appropriate dialysis time under a qualified dialysis system is recommended to obtain a spKt/V of 1.4. However, as the HEMO Study showed no improvement in morbidity and mortality with high-dose dialysis, increasing the dialysis dose beyond the recommended level is unnecessary.

The urea reduction ratio (URR) and equilibrated Kt/V (eKt/V) offer alternatives for assessing dialysis adequacy. The URR is simple and easy to calculate, but does not assess dialysis adequacy accurately because it does not take into account the volume of urea distribution. The eKt/V value is lower than that of spKt/V, because it is calculated by considering the redistribution of urea after dialysis. In the HEMO Study, the mean eKt/V in a standard group maintaining a mean spKt/V of 1.32 was 1.16. In general, the corresponding eKt/V is 1.2 when the targeting dialysis dose of spKt/V is 1.4.

Chapter 3. Dialysis membrane and modality for hemodialysis

Recommendation 3.1
We recommend the use of high-flux dialysis membranes in adult HD patients. However, the cost and availability of high-flux membrane need to be considered.
(Strong recommendation, high quality of evidence)

To date, three large-scale randomized clinical trials, the HEMO [43], MPO (Membrane Permeability Outcome) [44], and EGE [45] trials, have compared high- vs. low-flux HD membranes. These trials have not revealed a statistically significant benefit in reducing all-cause death.

However, the HEMO Study [43] reported a significant reduction of cardiovascular (CV) death as a secondary endpoint (0.072 vs. 0.059 patient-year), and a significant benefit in the composite outcome defined as CV death and hospitalization due to CV disease. Furthermore, a subgroup analysis showed a significant reduction of mortality risk by 37% in subgroup of patients treated with dialysis for more than 3.7 years prior to randomization. In the MPO Study [44], a statistically significant reduction in all-cause mortality was evident in the high-flux group compared to the low-flux group among participants with serum albumin equal to or lower than 4 g/dL (relative risk [RR], 0.49; 95% CI, 0.28–0.87). This study also showed that improved survival was associated with high-flux dialyzers among those with diabetes. Although the EGE Study [45] did not show a reduction of composite CV events, *post hoc* analysis suggested a benefit associated with high- vs. low-flux dialysis membrane on improving CV event-free survival among

those with AVFs and those with diabetes.

Meta-analysis of 12 prospective clinical trials [43–54] comparing high- vs. low-flux HD membranes, excluding observational studies, showed a 13% reduction (RR, 0.87; 95% CI, 0.76–0.99) in all-cause deaths and a 19% reduction (RR, 0.81; 95% CI, 0.70–0.95) in CV deaths. Furthermore, β2-microglobulin concentrations were reduced by 9.90 mg/L. However, no differences in hospitalization and Kt/V were shown.

Recommendation 3.2

1. There was no difference in all-cause mortality, CV mortality, hospitalization rate, and quality of life in online hemodiafiltration (HDF) compared with high-flux HD.
   (Conditional recommendation, moderate quality of evidence)
2. We consider it reasonable to apply high-volume online HDF after considering cost-effectiveness in some cases.
   (Expert consensus)

In randomized clinical trials comparing online HDF with high-flux HD, including the Turkish OL-HDF (Online Hemodiafiltration) [55] and the FRENCHIE (French Convective vs. Hemodialysis in the Elderly) [56], no significant effect on overall mortality and CV mortality was demonstrated. However, in the Turkish OL-HDF Study, which was divided into two groups with a 17.4 L (the median amount of supplementation) group and a high-efficiency group with 17.4 L or more, the latter experienced significantly reduced overall mortality rate ($p = 0.03$).

The ESHOL (Estudio de Supervivencia de Hemodiafiltración On-Line) Study [57], a randomized clinical trial comparing high-efficiency online HDF with HD, reported a 30% reduction in overall mortality (hazard ratio [HR], 0.70; 95% CI, 0.53–0.92; $p = 0.01$) and a 33% reduction in CV mortality (HR, 0.67; 95% CI, 0.44–1.01; $p = 0.06$) in the high-flow online HDF. Of the patients in the HD group, 8.1% used low-flux HD membranes.

In both the Turkish OL-HDF and FRENCHIE studies, no differences in overall hospitalization rates were observed between the two groups, but in the ESHOL Study, the hospitalization rate was lower in the high-flow online HDF group (RR, 0.78; 95% CI, 0.67–0.90; $p < 0.01$). In terms of quality of life, a meta-analysis performed on six prospective clinical trials, excluding observational studies [58–63], found no significant difference between the online HDF and HD groups.

Chapter 4. Anticoagulation for the hemodialysis

Recommendation 4.1

We recommend using unfractionated heparin (UFH) as the standard for systemic anticoagulation in HD patients without an increased bleeding risk because no differences could be found in the bleeding outcomes or circuit thrombosis between UFH and low-molecular-weight heparin (LMWH).
(Strong recommendation, low quality of evidence)

UFH is a conventional anticoagulant for HD in patients without active bleeding, a recent history of bleeding events, moderate to severe thrombocytopenia or heparin allergy. Typically, a loading dose of 1,000 to 2,000 units is administered at the start of HD, followed by a continuous infusion of 500 to 1,500 units per hour that is stopped approximately 30 minutes before the end of the HD session. The heparin dose can be adjusted empirically according to the clinical situation. Compared to UFH, LMWH, which can be administered as a bolus, has been shown to produce superior lipid profiles and less osteoporosis, and its use in HD patients in Europe is increasing [64]. We intended to verify whether LMWH could reduce bleeding events or HD circuit thrombosis compared to the conventional UFH in HD patients without higher bleeding risks.

Three meta-analyses that addressed the efficacy and safety of LMWH and UFH were identified at the time of literature search [65–67]. We selected clinical studies with parallel or cross-over designs that randomly allocated patients on HD or HDF into LMWH and UFH groups over a period of at least one month. Several studies were excluded from the analysis because of the following reasons: a less-than-1-week study period (Borm et al. [68], Koutsikos et al. [69] in the meta-analysis by Lim et al. [66] and Palamaner Subash Shantha et al. [67]); a dose-finding study design (Ryan et al. [70]); and no random allocation (Al-Saran et al. [71], Bramham et al. [72], Yang et al. [73] in a meta-analysis by Lazrak et al. [65], and Sabry et al. [74]). A meta-analysis was performed using six studies [75–80], although the poor blinding in these studies produced only moderate levels of evidence. The RR for any bleeding events was 0.74 (95% CI, 0.24–2.31), indicating no difference between the LMWH and UFH groups. The reported cases of major bleeding

were too low to perform subgroup analyses. Circuit thrombosis was defined as the number of cases of clotting in the dialyzer and circuit lines. Meta-analysis using three studies [76,77,79] resulted in an RR of 0.99 (95% CI, 0.56–1.77) for the LMWH group compared with UFH group, indicating no difference between the two anticoagulants. However, the level of evidence was assessed to be low due to heterogeneity among the studies and possible risks of bias.

Recommendation 4.2

1. We recommend not to use heparin for anticoagulation in HD patients with a high risk of bleeding.
   (Against recommendation, low quality of evidence)
2. We suggest using nafamostat mesylate, instead of heparin, for anticoagulation in HD patients with a high risk of bleeding.
   (Conditional recommendation, low quality of evidence)

Only a few studies conducted in Korea present low-level evidence for anticoagulation strategies for the HD patients with a risk of bleeding.

In a multi-center phase III trial assessing the influence of the anticoagulation efficacy and safety of nafamostat [81], 58 HD patients were considered to be at high risk of bleeding due to hemorrhagic complications, including postoperative status and gastrointestinal bleeding. Among 49 patients assessed during their clinical course, none experienced progression of preexisting hemorrhagic lesions while using nafamostat, and an improvement in preexisting lesions was evident in 37 patients (71%). In a cross-over arm involving the use of heparin in the same patients at preoperative stages or at recovery from hemorrhagic complication, aggravation of a preexisting lesion was observed in a single patient (4%); Only six patients (28%) experienced improvement in preexisting lesions, while 15 patients (68%) remained stationary. Nafamostat also proved to be superior to heparin in the degrees of residual blood in the dialyzer and blood clotting in the venous drip chamber. The incidence of adverse reactions was comparable in both groups.

In a randomized trial conducted in a single center in Korea [82], 17 HD patients with intracerebral hemorrhages were divided into two groups; one treated with heparin (n = 9), and the other with nafamostat (n = 8). Follow-up imaging of hemorrhagic lesions with computed tomography revealed that, compared with heparin, nafamostat significantly prevented the aggravation of preexisting hemorrhagic lesions (p = 0.02), while no specific descriptions of blood clots or the adverse events were presented.

Despite the lack of large-scale trials, we recommend not using heparin as an anticoagulant in HD patients with a high risk of bleeding, based on limited data that use of heparin may aggravate preexisting hemorrhagic lesions. Provided that regional anticoagulation with nafamostat efficiently prevents both aggravations of preexisting lesion and thrombosis in the extracorporeal blood circuits, we suggest the use of nafamostat, instead of heparin, for anticoagulation in HD patients at high risk of bleeding.

Chapter 5. Volume and fluid status in hemodialysis patients

Recommendation 5.1

1. We suggest that the weight-gain ratio between dialysis sessions not exceed 4% compared with the dry weight before dialysis.
   (Strong recommendation, moderate quality of evidence)
2. We consider it reasonable that patients whose body weight before dialysis exceeds 4% compared with the dry weight require an assessment of excess body fluids, dietary compliance, and nutritional status along with the provision of dietary education.
   (Expert consensus)

Excessive weight gain between dialysis sessions can lead to excess fluid volume and increase CV events and mortality by inducing excessive ultrafiltration [83,84]. However, because weight gain between dialysis sessions is indicative of adequate nutritional intake, nephrologists should use a multifactorial approach to the evaluation of patients with weight gain between dialysis sessions. Both the United States Renal Data System (USRDS) Study [85] and the DOPPS (Dialysis Outcomes and Practice Patterns Study) [86], large-scale observational studies in the early 2000s, reported that if the rate of weight gain between dialysis is excessively high compared to the dry weight, the risk of death is significantly higher than that of the control group. The USRDS Study reported that the risk of death was higher in patients with an interdialytic weight gain [IDWG] of >4.8% compared with a control group (IDWG ≤ 2.3%). For patients in the DOPPS, an IDWG of >5.7% was considered a high risk compared with an IDWG of ≤5.7%

in the control group. Based on these results, the 2015 dialysis treatment guidelines in Japan recommended a weight-gain ratio of less than 6% between dialysis sessions. However, the ultrafiltration rate per time of dialysis was not adjusted in these studies, the effect size of the mortality risk was small, and the definition of IDWG between dialysis sessions was not unified [83,84].

Weight gain between dialysis sessions is closely correlated with chronic volume overload, but the two concepts are not identical. Recent research suggests that, in patients with large weight gain during dialysis, there is a need to assess body-fluid levels simultaneously using different methods such as bioimpedance spectroscopy [87], correcting for anemia and nutritional status [88,89], and suggesting individualized approaches. The study included 38,614 HD patients who underwent total-body-fluid assessments. Even if the IDWG between dialysis was low (2.4% or less), the patients with chronic volume overload experienced significantly higher mortality [87]. As a result of the 2017 Japan DOPPS, in the group with a serum albumin level of 3.8 g/dL or less, the association with death was significant only in the group with a weight gain between dialysis sessions of less than 2.4% [88]. In a study by Lee et al. [90], the weight-gain ratio between dialysis sessions was 4.0% in a dialysis group compared with 2.0% in a control group, with the dialysis group showing a significant CV event risk with an HR of 1.93 compared with that of a control group after adjustment for residual renal function. In addition, the frequency of intradialytic hypotension during dialysis increased significantly from 3% or more of IDWG, and this phenomenon during dialysis was associated with death [91]. After an observational study of DOPPS on the effect of weight gain between dialysis sessions on prognosis was published in 2003, recent trends and prognosis of weight gain between dialysis sessions were published in 2017 [92]. The 2017 DOPPS study, which included approximately 22,000 patients, showed that, compared with results from 2003, the number of patients with a high rate of weight gain between dialysis sessions was decreasing. Nephrologists and dialysis staff should examine whether patients with excessive weight gain between dialysis sessions have poor compliance with a low-salt diet and water restrictions, and whether these cause excessive volume overload [86,93,94]. Conversely, patients with a low IDWG should be assessed for their nutritional status and need for greater intake.

Recommendation 5.2

We suggest that the change of conventional dialysate sodium (138–140 mEq/L) to low dialysate sodium (<138 mEq/L) to maintain adequate volume status. Attention should be paid to the possibility of developing intradialytic hypotension and muscle cramps while using low sodium dialysis.

(Conditional recommendation, moderate quality of evidence)

Sodium and water accumulation can lead to volume overload and hypertension, both of which are major risk factors for left ventricular hypertrophy [95–98]. In dialysis patients, antihypertensive drugs and ultrafiltration are the treatment of choice to remove volume overload, which is often not treated in clinical situations [99,100]. Katzarski et al. [101] reported that 90% of patients could control blood pressure without antihypertensive drugs if patients receive long HD (3 × 8 hours/week) and maintain an ideal healthy weight. In addition, some studies, which increased the frequency of dialysis to above usual levels, effectively controlled blood pressure, and edema and left ventricular hypertrophy were also improved [99,102,103].

However, increasing the frequency and duration of dialysis is subject to medical insurance restrictions. Lowering sodium dialysate levels below conventional levels is one method of removing sodium and water. Even at conventional sodium concentrations in dialysate, sodium moves back into the body, increasing blood pressure and water retention and leading to weight gain between dialysis [104]. According to a report studied in Korea, the sodium concentration of the dialysate was 140 mEq/L, 23%; 138 mEq/L, 64%; and 136, 137, and 139 mEq/L [105].

Recently, Dunlop et al. [106] published a meta-analysis comparing low sodium dialysate levels (Na of <138 mEq/L) to neutral conditions (Na of 138–140 mEq/L) and high sodium dialysate (Na of >140 mEq/L) in HD patients. This study shows that a low sodium dialysate level was associated with decreased weight gain, but increased risks of hypotension [106].

We conducted a literature search to compare the effects of conventional and low sodium dialysate on IDWG. Three randomized control studies and five before-and-after studies were reviewed [107–114]. We found that low dialysate sodium-reduced IDWG (mean difference [MD], –0.27kg; 95% CI, –0.57 to 0.17; p = 0.01), predialysis blood pressure (MD, –3.52; 95% CI, –5.46 to –1.57; p < 0.01) and use of antihypertensive medications (standardized MD, –0.60; 95%

CI, −1.13 to −0.07; p = 0.03). Low dialysate sodium was associated with low serum sodium concentration (MD, −1.59; 95% CI, −2.40 to −0.78; p < 0.01). The use of low sodium dialysate comes with increased side effects, such as hypotension, muscle cramps, and headaches during dialysis. The meta-analysis revealed that the frequency of hypotension during dialysis was significantly increased (RR, 1.49; 95% CI, 1.09–2.03; p = 0.01). This meta-analysis confirmed that low sodium dialysis solutions significantly reduced IDWG and blood pressure before dialysis compared with a group using conventional sodium dialysate.

Chapter 6. Blood pressure control in hemodialysis patients

Recommendation 6.1

1. There is insufficient evidence to assign optimal blood pressure target for HD patients.
   (Inconclusive, very low quality of evidence)
2. We consider it reasonable that antihypertensive medications should be prescribed for hypertensive HD patients considering multi-factors.
   (Expert consensus)

Lowering blood pressure significantly reduces CV morbidity and mortality rate in HD patients, which is a phenomenon similar to one associated with antihypertensive medications in the general population. However, no optimal blood pressure has been suggested [115]. Some traits require careful interpretation of the effects of lowering blood pressure. Most randomized controlled trials are based on a specific drug, not a target blood pressure. In a systematic review, it was difficult to pool blood pressure targets, because reductions in blood pressure achieved by patients varied widely among the trials, and also because baseline blood pressures were heterogenous among the studies. It is therefore insufficient to decide whether the effect of antihypertensive medication is from drug-specific effects or from reduced blood pressure under certain standards.

In one prospective observational cohort study performed in South Korea, a U-shaped HR pattern for patient mortality was observed among 2,299 HD patients over 4.5 median years of follow-up. The lowest risk was shown at 130–150 mmHg of systolic blood pressure. When continuous blood pressure was categorized, groups of patients with systolic blood pressure under 110 mmHg and over 170 mmHg were associated with an increased HR for mortality [116]. In a Western study based on 9,333 HD patients in an observational cohort with a median follow-up of 1.5 years, a similar U-shaped HR pattern of patient mortality was observed. However, the lowest risk was observed at close to 165 mmHg, which was different from the results of the Korean study [117]. Observational investigations of blood pressure and patient mortality among HD patients reported a U-shaped HR pattern, which represents an increased mortality risk at the tails of the blood pressure distribution. Nevertheless, this evidence is insufficient to suggest a consistent threshold of blood pressure at which an elevated mortality risk is likely. A multi-faceted approach is needed, because several factors can affect blood pressure treatment as confounders; these include interdialytic blood pressure variability [118], intradialytic antihypertensive drug removal through dialysis membranes [119], body-fluid changes [120], reduced vascular elasticity, and postdialysis blood pressure increment, which can also manifest as intradialytic hypertension [121].

Recommendation 6.2

We suggest lowering the dialysate temperature to reduce intradialytic hypotension.
(Conditional recommendation, moderate quality of evidence)

Intradialytic hypotension is a common complication and requires appropriate management because it affects the morbidity and mortality of HD patients. Several methods have been applied to the prevention of intradialytic hypotension. One is the lowering the dialysate temperature. Standard temperature dialysis typically involves maintaining the dialysate at 36.5°C–37.0°C, which is similar to body temperature. Methods that lower the dialysate temperature are dialysis with a fixed reduction of dialysate temperature (usually 35.0°C–35.5°C) and isothermic dialysis through body temperature monitoring using a biofeedback system [122].

According to seven randomized controlled trials [123–129] and three prospective studies [130–132], intradialytic hypotension incidence decreased when dialysis was performed by lowering the dialysate temperature [123–128,130,131]. Moreover, little change in blood pressure reduction was evident during or after dialysis, and the lowest blood pressure during dialysis was also higher than that of standard dialysis

[123,124,126–132]. These effects were more apparent in patients who experience more frequent intradialytic hypotension [127]. Lowering the dialysate temperature resulted in a decrease in the incidence of intradialytic hypotension, decreased regional left ventricular dysfunction, and myocardial stunning [123,129]. Cold sensations or discomfort tended to strengthen when the dialysate temperature was lowered; but not enough to stop dialysis [123,129], nor there was a difference in symptoms such as shivering [128]. Instead, studies have reported that patients felt more energetic with a lower dialysate temperature and requested reduction of the dialysate temperature in the future [127,131]. In previous studies, the dialysis efficiency, assessed by Kt/V and the URR, did not differ by dialysate temperature [127,128,130]. However, no direct comparison was made of the effects of dialysis between a fixed reduction of dialysate temperature and isothermic dialysate. Most studies of dialysate temperature were randomized cross-over trials conducted in a relatively small number of patients for a short period of time. In addition, no studies have been reported with long-term follow-up results on CV disease and mortality, and a large-scale study is needed to evaluate the major long-term outcomes according to dialysate temperature.

Chapter 7. Evaluating and monitoring hemodialysis patients

Recommendation 7.1

1. We consider it reasonable to test dialysis adequacy at least every 3 months in patients on maintenance HD.
   (Expert consensus)
2. We consider it reasonable to perform complete blood count tests, liver function tests, and routine chemistry tests at least monthly in patients on maintenance HD.
   (Expert consensus)
3. We consider it reasonable to test iron status, parathyroid hormone (PTH), and hemoglobin A1C (in diabetic patients) and perform a chest radiograph at least every 3 months in patients on maintenance HD.
   (Expert consensus)
4. We consider it reasonable to test hepatitis viral markers and perform electrocardiography at least every 6 months in patients on maintenance HD.
   (Expert consensus)

In patients undergoing HD, the purpose of dialysis is to remove uremic substances and water caused by CKD, and to control uremic symptoms, maintain stable electrolyte balance, and prevent deterioration of nutritional status, thereby improving health and quality of life. Maintaining an adequate dialysis dose means maintaining the patient's well-being, adequate volume status, and balanced biochemical levels. Multiple studies have reported that dialysis adequacy improves patient survival and quality of life [43,133–136]. However, no randomized controlled trials or prospective observational studies report outcomes for test items and intervals in patients on maintenance HD. Moreover, we found no studies of Korean patients on maintenance HD. However, in a recently published retrospective study in Canada, monthly routine blood testing in HD patients was not associated with a lower risk of death, CV events, or hospitalizations compared with testing every 6 weeks [137]. This guideline recommends performing a test as described above in accordance with expert opinion, considering that most dialysis centers conduct blood tests monthly.

Previously published foreign practice guidelines recommend that dialysis doses be measured monthly, as most dialysis centers perform blood tests, including those for electrolytes, monthly and as tests performed in patients undergoing maintenance HD are uncomplicated and inexpensive [138,139]. The KDOQI guideline published in 2006 recommended that the dialysis dose be measured at regular intervals of no less than monthly (A). Less-frequent measurements may compromise the timeliness with which deficiencies in the delivered dose of HD are detected and therefore may delay implementation of corrective action [138]. European best practice guidelines published in 2007 also recommend that delivered dialysis doses should be measured at least monthly (opinion) [139]. The UK Renal Association CPG published in 2019, recommends measuring and monitoring dialysis doses on a monthly base for the majority of center-based dialysis patients (1B) [64]. However, in this guideline, we recommended that dialysis doses be measured at least every 3 months according to expert agreement, taking into account the medical reality and cost of testing in Korea.

In this guideline, monthly complete blood counts, liver function tests (including total protein and albumin levels), and routine blood chemistry (blood urea nitrogen, creat-

inine, sodium, potassium, calcium, phosphate, uric acid, and glucose) are recommended. Most HD centers in Korea perform blood tests monthly. Moreover, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) CPG for anemia in CKD recommends measuring hemoglobin concentrations at least monthly in patients with grade 5 CKD [140]. This guideline recommends applying those guidelines to Korean patients on maintenance HD, according to expert agreement.

The KDIGO 2017 CPG update for CKD-mineral bone disorder states that it is reasonable to monitor PTH levels every 3–6 months in patients with grade 5 CKD [141,142]. We recommend monitoring PTH levels at least every 3 months, according to expert agreement in this guideline. As other guidelines, including the KDIGO, suggest screening for hepatitis virus infection in patients on dialysis every 6 months [143–145], this guideline recommends screening for hepatitis viral markers at least every 6 months, according to expert agreement in this guideline.

Chapter 8. Nonstandard setting of hemodialysis (elderly, children)

Recommendation 8.1

1. We suggest that preparation for appropriate renal replacement therapy be considered for elderly patients who progress to ESKD.
   (Conditional recommendation, moderate quality of evidence)
2. We consider it reasonable that in elderly patients with ESKD, the optimal treatment should find an individualized balance between appropriate renal replacement therapy and conservative treatment.
   (Expert consensus)

With the advancement of renal replacement therapy, the overall survival rate of patients with ESKD is improving, but it is not yet clear whether renal replacement therapy offers any survival benefit in elderly patients compared with conservative treatment. Although randomized control studies are not available due to the nature of the study, comparing the dialysis group with the conservation treatment group makes it difficult to compare the selection bias of elderly patients with a relatively healthy group, the lead-time bias of the patients with dialysis, and the lack of studies of patients who perform conservative treatment. A meta-analysis of 89 observational studies from 1976 to 2014 on elderly patients with ESKD, including a total of 294,921 patients, reported a 1-year survival rate of 77.9% in the HD group and 70.6% in the conservative treatment group. Although the report that HD may have some benefits [146], it was unable to judge the role of conservative treatment because only 724 patients (0.2%) were included in the conservative treatment group. In a 2017 meta-analysis, the dialysis group showed a superior survival rate compared with the conservative treatment group (HR, 0.53; 95% CI 0.30–0.91; p = 0.02), but there was significant heterogeneity among studies [147]. Most of the studies before 2010 included in the meta-analysis were small and retrospective studies [148–150], and one small prospective study did not distinguish HD from peritoneal dialysis [151].

In prospective observational studies of elderly patients after 2015, dialysis treatment was associated with benefits compared with conservative treatment in entire patient groups [152–154], although comorbidities increased [152] and the benefit was not significant in patients older than 85 years [153] or 80 years [154]. In retrospective studies, the benefit of dialysis was greater than that of conservative treatment, but setting an appropriate control group would be important [155–157]. A Canadian study of reimbursement data using propensity-score matching showed a benefit of dialysis in the first 3 years (HR, 0.59; 95% CI, 0.46–0.77; p < 0.01), but no difference between dialysis and conservative treatment was found after 3 years [157]. In this practice guideline, we conducted a meta-analysis of 11 studies in which the mean age of elderly patients in the dialysis group was 76.0 ± 5.3 years. The meta-analysis showed that dialysis was more beneficial regarding survival than conservative treatment in elderly patients (HR, 0.42; 95% CI, 0.37–0.47; p < 0.01). As the evidence for survival gain by dialysis treatment grows [158,159], preparations for appropriate renal replacement therapy are needed when elderly patients progress to ESKD.

Recommendation 8.2

1. For HD of children younger than 5 years old, we consider it reasonable that the minimal nurse-to-patient ratio be 1:1.
   (Expert consensus)
2. For HD of older children, we consider it reasonable that the minimal nurse-to-patient ratio be 1:2.
   (Expert consensus)

Dialysis in infants and children requires exceptional skill and expertise. Pediatric HD requires devices appropriate for the patient's body size, neonatal or pediatric dosages of medications, proper management of vascular access problems, and meticulous monitoring of volume status and vital signs. Infants and young children undergoing HD are sensitive to small changes in body water volume or blood pressure because their effective blood volume is smaller than that of adults [160]. As children may not recognize or verbally express the symptoms of side effects of HD, vital signs should be measured more frequently, and patients need to be monitored more carefully than adults during pediatric HD. For safe HD in children, more frequent clinical assessment is necessary [161] and often requires a nurse-to-patient ratio of 1:1 [162]. While there has been no CPG [163], a survey of clinical practices in the UK reported that a typical nurse-to-patient ratio was 1:1 for HD in children younger than 5 years old and 1:2–1:3 in the case of older children at most centers [164]. For HD in young children or patients with significant neurocognitive disability, a nurse-to-patient ratio of 1:1 is required. An infant may need the care of two nurses. HD requiring isolation also needs one nurse for each patient. For children who can communicate or adolescents whose development is normal, a nurse-to-patient ratio of 1:2 may be safe. For pediatric dialysis, there should be at least two registered nurses per duty, and a nurse-to-patient ratio should be 1:2 or higher [165].

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Access to the full-text version

The full-text version of this CPG is available on the KSN website (http://www.ksn.or.kr, http://krcp-ksn.org)

Conflicts of interest

All authors have no conflicts of interest to declare. The Work Group has been making the best efforts to avoid any actual and potential conflicts of interest to ensure a neutral and fair process in guideline development. All members of the Work Group obtained a conflict-of-interest disclosure form before participating in the development of the CPG and when completing the CPG to determine whether there was a financial or non-financial conflict of interest. In the case of reports of corporate research sponsorship or consulting, detailed report contents were confirmed after review by the Work Group. To determine whether the amount of money and the content of the recommendation can be affected, and if an amount exceeding the standard may affect the content of the recommendation, we recommend that the opinion of the relevant member be excluded when determining the direction and strength of the recommendation. This principle was applied from the beginning to the end of the development.

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