Dialysis Indication and Initiation Time for Dialysis

1

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1.1 Background

1.1.1 Kidney Functions

Kidneys have many functions to maintain internal milieu of aqueous phase. These include maintenance of hydration status, electrolyte concentration, and acid-base status and excretion of endogenous or exogenous wastes. Moreover, kidneys also produce several hormones.

On the other hand, some chronic kidney disease (CKD) patients eventually develop end-stage renal disease (ESRD), which requires some artificial support for the kidney functions. In general, most of kidney functions deteriorate in same paces as the glomerular filtration rate (GFR) declines in the patients. Therefore, many nephrologists consider the indication of dialysis initiation by estimated GFR (eGFR) values (van de Luijtgaarden et al. 2012).

The exact measurement of GFR involves complicated processes. Thus, in patients with earlier stage of CKD, eGFR calculated from creatinine or cystatin-C, age, gender, and race (Levey et al. 1999, 2006, 2009) is widely used to determine CKD staging (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013). However, creatinine has a limitation that the serum levels are influenced by muscle mass or the amount of meat that the patients ate as their foods. Therefore, the patients with reduced muscle mass or appetite which is prevalent among older population experienced lower serum creatinine levels compared to those who have the same GFR but sufficient muscle mass (Grootendorst et al. 2011). Actually, those who have higher production or urinary excretion of creatinine tended to demonstrate lower eGFR compare to creatinine clearance (Beddhu et al. 2003). Therefore, eGFR can potentially underestimate the actual GFR among such population, vice versa.

The significance of measured GFR can be illustrated by the following evidences. A study from NECOSAD (The Netherlands Cooperative Study on the Adequacy of Dialysis), a cohort of incident dialysis population performed in the Netherlands, demonstrated that eGFR overestimated measured GFR (mGFR; mean of creatinine and urea clearance) by 0.8 mL/min/1.73 m^2, and the limits of agreements were −4.1 to 5.6 mL/min/1.73 m^2. In this study, higher measured clearance was not associated with the worse outcome, while higher eGFR was associated with worse outcome. Moreover, eGFR was shown to relate with the muscle mass (Grootendorst et al. 2011).

A meta-analysis indicated the significance of measured GFR and demonstrated that higher measured GFR related to better survival (adjusted

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HR 0.801), although the higher eGFR related to worse outcome (AHR 1.038) (Susantitaphong et al. 2012).

Taken together, measured clearance might be helpful to consider the indication of dialysis initiation, although the measurement itself requires collection of urine.

Several investigations employed the average of creatinine and urea clearances (Dombros et al. 2005). The author considers the direct measurement of clearances is required to test the patient's true kidney function not from the estimation.

1.1.2 Historical Perspectives of the Timing of Dialysis Initiation

Historically, the earlier initiation of dialysis treatment was recommended, because the early initiation of dialysis shortens the period during which the patients experience uremic circumstances. Such early initiation of dialysis was considered to improve survival or quality of life by preventing uremic complications (Dombros et al. 2005; Bonomini et al. 1985; Perrone et al. 1992; Churchill 1997; Tattersall et al. 1995; Hakim and Lazarus 1995). Bonomini et al. investigated the outcome of 390 incident patients. Among them, 82 patients started dialysis early (mean creatinine clearance of 11 mL/min), because they manifested uremic symptoms refractory for medication, were unable to follow low-protein diet, or adopted early dialysis voluntarily. On the other hand, remaining 308 patients were treated by low-protein diet conservatively for 24–53 months and then started their dialysis therapy at the time of their Ccr of 2.1–4.8 mL/min. They found that the patients in early-start group experienced higher survival and full-time working rate and lower hospitalization rate compared to those in late-start group (Bonomini et al. 1985). Thus they concluded that early start of dialysis is beneficial for patients' conditions after start of dialysis therapy.

From such evidences, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guideline recommended early start of dialysis therapy in terms of GFR. The guideline published in 2006 told the value of eGFR from where dialysis therapy is considered should be 15 mL/min/1.73 m^2 (Initiative NKFKDOQ 2006), while the guideline in 1997 told 10.5 mL/min/1.73 m^2 (National Kidney Foundation (NKF-DOQI) 1997). As a result, the eGFR at the initiation of dialysis therapy had been becoming higher in the United States. In 1996, only 19% of the patients started their dialysis with their eGFR more than 10 mL/min/1.73 m^2, but 45% of incident patients started dialysis with eGFR more than 10 mL/min/1.73 m^2 in the year 2005 and (Rosansky et al. 2009). O'Hare, et al. demonstrated that the dialysis started earlier by 147 days from 1997 to 2007. The differences were more pronounced for older population. The patients 75-year-old or more started dialysis earlier by 233 days during the past 10 years (O'Hare et al. 2011). Also in Canada, the similar trend had been observed (Clark et al. 2011).

1.2 Current Considerations About Dialysis Initiation

1.2.1 Early Dialysis Initiation Is Not Favorable

However, many evidences, most of them are epidemiological and observational studies, against early initiation have been published since late 1990s. For example, the results from Dialysis Morbidity Mortality Study Wave II in the United States demonstrated that HR for survival was 1.14 ($p = 0.002$) per 5 mL/min/1.73 m^2 of higher eGFR at the initiation (Beddhu et al. 2003). Similarly, the results from Centers for Medicare and Medicaid Services indicated that the patients who started dialysis with eGFR more than 10 mL/min/1.73 m^2 experienced significantly poorer survival (HR 1.42) compare to those with eGFR less than 5 mL/min/1.73 m^2 (Kazmi et al. 2005).

Also from European countries, many studies showed that higher eGFR at the initiation related to worse outcome. The results from the registry of European Renal Association and European

Dialysis Therapy Association investigated the relationship between eGFR at the initiation and subsequent survival. They found that higher eGFR was associated worse survival (HR 1.02, 95%CI: 1.01–1.04 per 1 mL/min/1.73 m^2 higher eGFR) (Stel et al. 2009).

Moreover, in Asian countries, similar findings have been obtained. In Japan, the averaged eGFR is lower than other countries. The results of the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR) indicated that mean eGFR was 6.52 mL/min/1.73 m^2 and only 10.6% of total population started their dialysis treatment with eGFR more than 10 mL/min/1.73 m^2 in 2007 (Yamagata et al. 2012a). Among such population, Yamagata et al. demonstrated that the patients with eGFR more than 8 mL/min/1.73 m^2 experienced worse 1-year survival compared to those with eGFR between 4 and 6 mL/min/1.73 m^2. HR for eGFR of 8–10 mL/min/1.73 m^2 group was 2.20 (95%CI 1.52–3.17) after adjustment. Moreover, they found that eGFR less than 2 mL/min/1.73 m^2 tended to be associated with worse survival (HR 3.40, 95%CI 0.98–11.8) (Yamagata et al. 2012a). Hwang et al. investigated the data of Taiwan and also found that lowest quintile of eGFR (eGFR <3.29 mL/min/1.73 m^2) at initiation of dialysis was associated with better subsequent 1-year survival (Hwang et al. 2010).

Meta-analyses published to date also demonstrated that earlier dialysis initiation was associated with worse outcomes (Susantitaphong et al. 2012; Pan et al. 2012; Slinin et al. 2015). One meta-analysis investigated the results of 15 observational studies. They found that 1 mL/min/1.73 m^2 higher eGFR was associated with higher mortality [HR 1.037, 95%CI 1.030–1.045], and the results did not differ after adjustment of nutritional markers (Susantitaphong et al. 2012). Another meta-analysis investigated ten observational studies and one randomized control trial which will be discussed later. They also found that early dialysis initiation related to higher mortality [OR 1.33, 95%CI 1.18–1.49] (Pan et al. 2012). Recently, another meta-analysis of 19 trials was performed to form an evidence for NKF KDOQI guideline. In this meta-analysis again, the patients with estimated creatinine clearance (eClcr) of 10–14 mL/min/1.73 m^2 did not experience better survival compared to those with eClcr of 5–7 mL/min/1.73 m^2 (Slinin et al. 2015). Moreover, a meta-analysis that investigated such relationship only among diabetic patients also failed to demonstrate the superiority of early dialysis initiation (Nacak et al. 2016).

From these results, across races or ethnicities, the concept that early dialysis initiation can lead to better clinical outcome after dialysis initiation is now questioned. However, the observational studies cannot eliminate biases such as immortal-time bias, lead-time bias (Sjolander et al. 2011), or others (Mehrotra et al. 2013). Therefore, randomized control trials had been anticipated to investigate the timing of dialysis initiation and subsequent clinical outcomes.

1.2.2 The Initiating Dialysis Early and Late (IDEAL) Study

Under such circumstances, the Initiating Dialysis Early and Late (IDEAL) study was planned (Cooper et al. 2004) and performed (Cooper et al. 2010). IDEAL study is the only randomized control trial to investigate the timing of dialysis ever. The study recruited 828 CKD patients (mean age of 60.4 years old and 355 of them were diabetic) with their eGFR of 10–15 mL/min/1.73 m^2 by Cockcroft-Gault equation. The patients were randomized into two groups; one group started dialysis at eGFR of 10–14 mL/min/1.73 m^2 (early-start group), and the other started at eGFR of 5–7 mL/min/1.73 m^2 (late-start group). Primary endpoint was set as all-cause mortality. The time period from randomization to actual initiation of dialysis was 1.80 (95%CI 1.60–2.23) months for early-start group and 7.40 (95%CI 6.23–8.27) months for late-start group. During the median follow-up period of 3.59 years, 152 patients (of 404 patients, 37.6%) in early-start group and 155 patients (of 424 patients, 36.6%) in late-start group were deceased. The HR of death for early-start group was 1.04 (95%CI 0.83–1.30, $p = 0.75$) compared to late-start group. Other endpoints of cardiovascular disease,

infection, or other complications were also comparable between two groups. Therefore, this study did not demonstrate the superiority of early start and failed to show the advantage of late start at the same time. However, some limitations have been pointed out for this study. The most important is 75.9% of the patients in late-start group started their dialysis before their eGFR reached 7.0 mL/min/1.73 m^2 due to mostly uremia (72.7% of those started earlier in late-start group), while 18.6% in early-start group started their dialysis eGFR below 10 mL/min/1.73 m^2. Such high proportion of protocol violation makes this study difficult to be assessed. Nonetheless, IDEAL study told us that the timing of starting dialysis cannot be determined solely by eGFR. Thus close monitoring the uremic symptoms of the patients including other conditions is warranted for determining the initiation of dialysis.

Moreover, several post hoc analyses have been published about IDEAL study. One of the studies compared the medical costs and quality of life between two groups. The study demonstrated that the medical costs were higher among the patients who were allocated to the early-start group, while the quality of life did not differ between the groups (Harris et al. 2011). Another study investigated the effect of timing only among the planned hemodialysis patients. This study again did not show the advantage of early initiation (Collins et al. 2011). These facts also discouraged the advantage of early initiation of dialysis treatment.

1.3 Factors To Be Considered for the Initiation of Dialysis

1.3.1 Uremic Symptoms

As discussed above, there is little evidence by which we can set the specific eGFR value for dialysis initiation, although many nephrologists rely on the eGFR value in decision-making to start dialysis treatment, especially for the uncomplicated patients (van de Luijtgaarden et al. 2012). Therefore, during the process of actual dialysis initiation, we should consider the entire clinical picture of the patients and should make clinical judgment (Weiner and Stevens 2011). In Japan, the guideline published in 1991 demonstrated a systematic list of the signs or symptoms observed in uremia (Kawaguchi and Mimura 1991), and these criteria were also utilized by the current Japanese guideline on initiating hemodialysis (Watanabe et al. 2015). Table 1.1 shows these uremic symptoms demonstrated by this guideline. Table 1.2 indicates the symptoms and signs of uremia described in NKF KDOQI hemodialysis adequacy guideline 2015 update (National Kidney Foundation 2015). DOPPS data demonstrated that higher mortality can be observed soon after hemodialysis initiation (Bradbury et al. 2007). Specifically, the incident hemodialysis patients experience higher mortality due to heart failure. Therefore, overhydration can be related to worse outcomes among the uremic symptoms. The fact was also evidenced by the study on JRDR. Yamagata et al. investigated the relationship between the symptom at the initiation of dialysis and subsequent survival. They found that congestive heart failure, intractable edema, oliguria, and unrecovered acute exacerbation of renal function were related to higher mortality, and HR for them were 1.87 (95%CI 1.47–2.38), 1.91 (95%CI 1.44–2.54),

Table 1.1 Uremic signs and symptoms listed in the Japanese guideline in 1991

Category	Signs and symptoms
Fluid accumulation	Anasarca, severe low proteinemia, lung congestion
Electrolyte disturbance	Refractory electrolyte and/or acid-base disturbances
Gastrointestinal symptoms	Nausea, vomiting, appetite loss, diarrhea, or others
Circulatory abnormalities	Severe hypertension, heart failure, pericarditis
Neurological symptoms	Central and/or peripheral nervous disorders, psychosis
Hematological symptoms	Severe anemia, bleeding diathesis
Visual disturbance	Uremic retinopathy, diabetic retinopathy

Adapted from Kawaguchi and Mimura (1991)

Table 1.2 Uremic symptoms and signs described in NKF KDOQI guideline in 2015

Symptoms
Fatigue
Lethargy
Confusion
Anorexia
Nausea
Alterations in senses of smell and taste
Cramps
Restless legs
Sleep disturbances
Pruritus
Signs
Seizures/change in seizure threshold
Amenorrhea
Reduced core body temperature
Protein-energy wasting
Insulin resistance
Heightened catabolism
Serositis (pleuritis, pericarditis)
Hiccups
Platelet dysfunction
Somnolence

Adapted from National Kidney Foundation (2015)

1.64 (95%CI 1.19–2.25), and 2.74 (95%CI 1.94–3.88), respectively (Yamagata et al. 2012b). Another study investigated the association of signs and symptoms with early dialysis initiation among nursing home residents (Kurella Tamura et al. 2010). They evaluated seven clinical signs and symptoms: dependence in activities, cognitive impairment, edema, dyspnea, nutritional problems, vomiting, and body size. They found that the patients who manifested more signs and symptoms significantly more likely start dialysis at their eGFR of 15 mL/min/1.73 m^2 or higher (OR 1.16 per symptom, 95%CI 1.06–1.28).

1.3.2 Nutritional Indications

Deterioration of nutritional status has been one of the reasons for dialysis initiation. Certainly, most of guidelines (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013; National Kidney Foundation (NKF-DOQI) 1997; Watanabe et al. 2015; National Kidney Foundation 2015; European Best Practice Guidelines Expert Group on Hemodialysis ERA 2002; Tattersall et al. 2011; The CARI guidelines 2005a; Warwick et al. 2014; Churchill et al. 1999) in their statements recommended dialysis initiation when the patients experience the deterioration of nutritional status that can be attributable to uremia. However, the actual descriptions about malnutrition to make nephrologists consider dialysis initiation are diverse. The early guidelines, NKF KDOQI 1997 and CSN 1999, recommended normalized protein equivalent of nitrogen appearance (nPNA) to use and to initiate dialysis if nPNA falls below 0.8 g/kg/day spontaneously (National Kidney Foundation (NKF-DOQI) 1997; Churchill et al. 1999). CNS 1999 guideline mentioned subjective global assessment as an index of malnutrition (Churchill et al. 1999). The latest NKF KDOQI 2015 guideline mentioned protein-energy wasting as one of the signs to be monitored closely (National Kidney Foundation 2015). On the other hand, other guidelines did not specifically tell about the indices to monitor in their statements (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013; Watanabe et al. 2015; European Best Practice Guidelines Expert Group on Hemodialysis ERA 2002; Tattersall et al. 2011; The CARI guidelines 2005a; Warwick et al. 2014). Although the guidelines told that malnutrition is one of the signs to initiate dialysis, the detailed criteria for dialysis initiation remain to be investigated. Therefore, the nutritional status of CKD patients should be assessed globally from such indices as SGA, lean body mass, serum albumin, PNA, or other indices (Kalantar-Zadeh et al. 2001).

Nonetheless, the proportion of the patients who have PEW are quite high, and it can be related to subsequent worse survival (de Mutsert et al. 2008). Therefore, the nutritional management on the advanced CKD, especially those preventing PEW, is required to attain better clinical outcomes. Once the patients develop decline in nutritional status that is resistant for dietary therapy, we should start dialysis therapy properly.

1.3.3 Comorbidities

Obviously, the compelling reasons for dialysis initiations such as overhydration or congestive heart failure independent of patients' GFR worsen the prognoses afterward. Several studies have elucidated this point. A study from France investigated the association of eGFR at the initiation of dialysis with subsequent survival. The higher mortality was observed among those with higher eGFR by crude model (HR 1.40, 95%CI 1.36–1.45). However, the association was attenuated (HR 1.08, 95%CI 1.04–1.12) by adjustment for comorbidities, mobility, and nutritional status as well as age and gender. The fact indicated that age or comorbidities affected the association of higher eGFR and mortality partly but not entirely (Lassalle et al. 2010). Moreover, the frailty among CKD population comes to draw attentions. Among the incident dialysis population, the proportion of the patients with frailty was reportedly as high as 73%. The frail population significantly related to higher eGFR at dialysis initiation and poorer survival (Bao et al. 2012). These evidences remind us that the patients who started dialysis early might be forced to start early by compelling reasons due to comorbidities. To elucidate this association, Rosansky et al. investigate the effects of eGFR at initiation only among the "healthiest" population with serum albumin ≥3.5 g/dl. But they found that the association of higher eGFR and worse outcome was not changed even among such healthiest population (Rosansky et al. 2011). Another study on older population was also performed on the United States Renal Data System (USRDS) database. They investigated the association of eGFR values at initiation and subsequent survival for up to 3 years. The results indicated that higher eGFR (≥ 10 mL/min/1.73 m^2) was associated with poorer prognosis even after rigorous adjustment for patients' health status and it was consistent across subgroups (Crews et al. 2014). Therefore, comorbidities can affect the outcome but not entirely.

1.3.4 Speed of Decline of Renal Function

Recently, the rate of decline of renal function reportedly associates with the incidence of ESRD among pre-dialysis CKD population (Kovesdy et al. 2016). The rate of decline in eGFR before dialysis initiation has been reported to relate with the survival after start of dialysis therapy. O'Hare et al. investigated the trajectories of eGFR decline and subsequent clinical outcome among incident dialysis patients. They reported that steeper eGFR decline was associated with higher mortalities during the first year of dialysis and higher probabilities of hospitalization or diagnoses of AKI (O'Hare et al. 2012). Similarly, several studies demonstrated that abrupt (Hsu et al. 2016) or even faster (Browne et al. 2014; Ramspek et al. 2016) decline of eGFR was associated with higher mortality during short (Hsu et al. 2016) or longer periods (Browne et al. 2014; Ramspek et al. 2016). Interestingly, a study from NECOSAD demonstrated such relationship could only be observed with mGFR but not with eGFR (Ramspek et al. 2016). CKD is one of the major risk factors for AKI requiring dialysis (Hsu et al. 2008). Thus we can imagine that such abrupt or steeper renal function decline is related to the acute on chronic renal failure. We should pay special attentions for patients who experience faster decline of renal function to prevent vicious cycles worsening clinical outcomes.

1.3.5 Facility Characteristics

Clinical practice patterns of facilities might be associated with the timing of initiation. Margaret et al. investigated eGFR values for veterans who initiated within versus outside the Veteran Affairs (VA) medical centers. They found that the patients less likely started dialysis at eGFR ≥10.5 mL/min/1.73 m^2 within the VA medical centers compared to outside of the VA facilities (Yu et al. 2015). This observation was confirmed by another study which investigated the average eGFR at initiation of dialysis within 804 health service areas

in the United States. The study found that there was wide variety in mean eGFR values and only 11% of variation was explained by the patient characteristics (Scialla et al. 2014). On the other hand, a Canadian study investigates the proportion of the patients with eGFR of 10.5 mL/min/1.73 m^2 or more at the initiation of dialysis across the regions. They found that a large heterogeneity existed for the proportion by regions investigated. However, only 3.1% of variabilities could be attributed to the facility, while remaining 96.9% was attributed to patient factors (Sood et al. 2014).

1.3.6 Other Clinical Indicators

Many researchers have developed clinical scores that predict mortality after initiation of dialysis. For this purpose, Charlson's comorbidity index (CCI) (Charlson et al. 1987) has historically been used. However, this index was developed for the patients on admission to predict 1-year survival and was not developed for the incident dialysis population. Park et al. developed modified CCI from the Korean incident dialysis population of 24,738 patients, and they found that the index had improved predictive power of 6-month, 1-year, and 2-year survival compared to the original CCI (Park et al. 2015). Doi et al. also developed an equation to predict 1-year mortality among incident dialysis population. They found that eGFR, albumin, calcium, modified CCI, performance status, and ESA use were associated with the survival (Doi et al. 2015). These indices clearly indicate that we should pay attentions not only to the patients' laboratory data or clinical symptoms but also the comorbidities of the patients. Thereby, they provide the opportunity to improve the outcomes of the incident patients.

1.4 Published Guidelines

From the evidences above described, many guidelines have been published regarding the timing of initiation of dialysis (Table 1.3).

Table 1.3 The indications of dialysis initiation described in each guideline (National Kidney Foundation 2015; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013; Working Group Committee for Preparation of Guidelines for Peritoneal Dialysis Japanese Society for Dialysis Therapy, Japanese Society for Dialysis Therapy 2010; Watanabe et al. 2015; Tattersall et al. 2011; The CARI guidelines 2005a, 2005b; Warwick et al. 2014; Churchill et al. 1999)

		The first-line indications of dialysis	Renal function from which dialysis is indicated	Renal function for dialysis initiation without uremic symptom
NKF KDOQI	2015	Signs and/or symptoms associated with uremia Evidences of protein-energy wasting Inability to safely manage metabolic abnormalities and/or volume overload with medical therapy	Not specified	No specific GFR
KDIGO	2012	Symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus) Inability to control volume status or blood pressure Progressive deterioration in nutritional status refractory to dietary intervention Cognitive impairment	Not specified but conditions requiring dialysis initiation often but not invariably occur in the GFR range between 5 and 10 mL/min/1.73 m^2	Not specified
JSDT	2009	Signs or symptoms of uremia resistant to medical treatment	GFR < 15.0 mL/min/1.73 m^2	GFR < 6.0 mL/min/1.73 m^2

(continued)

Table 1.3 (continued)

		The first-line indications of dialysis	Renal function from which dialysis is indicated	Renal function for dialysis initiation without uremic symptom
	2013	Uremic signs and symptoms (see Table 1.1) Malnutrition Deterioration of ADL	GFR < 15.0 mL/min/1.73 m^2 Maximal pre-dialysis medication should be undertaken until GFR < 8	GFR < 2 mL/min/1.73 m^2
EBPG	2011	Symptoms or signs of uremia Inability to control hydration status or blood pressure Progressive deterioration in nutritional status	GFR <15 mL/min/1.73 m^2 (majority of the patients will be symptomatic in the range 9–6 mL/min/1.73 m^2)	No specific GFR but asymptomatic patients may benefit from a delay in starting dialysis in order to allow preparation, planning, and permanent access creation rather than using temporary access In high-risk patients or the patients who cannot be monitored uremic symptoms closely, a planned start to dialysis while still asymptomatic may be preferred
KHA-CARI	2005	Evidence of uremia or its complications such as malnutrition	GFR falls below approximately 10 mL/min/1.73 m^2 (occasionally, patients may require to initiate dialysis at a higher GFR)	GFR falls below approximately 6 mL/min/1.73 m^2
UK	2013	Careful discussion with the patient of the risks and benefits of RRT Symptoms and signs of renal failure Deterioration of nutritional status Comorbidity Functional status Physical, psychological, and social consequences of starting dialysis	CKD stage 5 (eGFR <15 mL/min/1.73 m^2)	Not specified
CSN	1999	Symptoms or signs of uremia Evidence of malnutrition nPNA < 0.8 g/kg/d or clinical malnutrition by SGA, dialysis initiation is recommended	GFR is less than 12 mL/min	GFR is less than 6 mL/min

NKF KDOQI, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guideline; *KDIGO*, Kidney Disease: Improving Global Outcomes; *JSDT*, the Japanese Society for Dialysis Therapy guidelines; *EBPG*, European Best Practice Guidelines; *KHA-CARI*, Kidney Health Australia Caring for Australasians with Renal Impairment; *UK*, the Renal Association guidelines in the United Kingdom; *CSN*, the Canadian Society of Nephrology; *GFR*, glomerular filtration rate; *ADL*, activity of daily living; *CKD*, chronic kidney disease; *RRT*, renal replacement therapy; *nPNA*, normalized protein equivalent of nitrogen appearance; *SGA*, subjective global assessment

1.4.1 NKF KDOQI Guidelines

Since 1997, the National Kidney Foundation in the United States has published guidelines periodically. The timing of initiation of dialysis therapy has been one of the most important topics of this guideline.

In the guidelines for peritoneal dialysis adequacy published in 1997, the description about the timing for initiating dialysis was included (National Kidney Foundation (NKF-DOQI) 1997). The guideline employed two parameters of renal urea clearance and normalized urea appearance, the proxy of protein intake. The

patients should be advised to initiate dialysis when the weekly renal Kt/Vurea falls below 2.0, which is equivalent to urea clearance of 7 mL/min, creatinine clearance of 9–14 mL/min/1.73 m^2, and GFR of 10.5 mL/min/1.73 m^2. Dialysis should also be started when nPNA spontaneously falls below 0.8 g/kg/day despite of intervention by a registered dietitian.

However, in 2006 the update version of hemodialysis adequacy guidelines recommended higher GFR values to consider dialysis initiation (National Kidney Foundation Kidney Disease Outcome Quality Initiative 2006). The guideline says when patients reach stage 5 CKS (eGFR <15 mL/min/1.73 m^2), nephrologist should evaluate the benefits, risks, and disadvantages of beginning kidney replacement therapy. Particular clinical considerations and certain characteristic complications of kidney failure may prompt initiation of therapy before stage 5.

The current version was published in 2015 (National Kidney Foundation 2015). This version changed the description about the timing of dialysis initiation dramatically. They underscore the importance of signs and symptoms and removed the concrete value of GFR for considering dialysis initiation. The guideline says: The decision to initiate maintenance dialysis should be based primarily upon an assessment of signs and/or symptoms associated with uremia, evidences 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. The rationale for this recommendation emphasized two points. One is that dialysis initiation should not base solely on measurements of kidney function especially in asymptomatic patients. The other is that dialysis initiation should not be denied to patients with signs or symptoms which can be managed by dialysis, simply because the GFR is considered too high.

1.4.2 Kidney Disease: Improving Global Outcomes (KDIGO) Guideline

Kidney Disease: Improving Global Outcomes (KDIGO) published CKD guideline in 2013 (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013). The guideline describes the timing of renal replacement therapy (RRT) initiation. This guideline was also made after the results of IDEAL study were published. Therefore, the appearance of signs or symptoms was emphasized. It says that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, and pruritus), inability to control volume status or blood pressure, a progressive deterioration in nutritional status refractory to dietary intervention, or cognitive impairment. The guideline only mentions GFR by saying that these conditions often but not invariably occur in the GFR range between 5 and 10 mL/min/1.73 m^2.

1.4.3 Japanese Guidelines

Historically, in 1972 the Ministry of Health and Welfare in Japan started covering dialysis therapy by healthcare insurance. At that time, the committee in the Ministry determined criteria for dialysis therapy. The criteria determined that dialysis therapy is indicated when uremic symptoms are refractory for medical treatments and deteriorate patients' daily activities. The concrete indices included clinical symptoms (oliguria or nocturnal polyuria, insomnia and/or headache, nausea and/or vomiting, renal anemia, severe hypertension, and hypervolemia), decreased renal function (i.e., creatinine clearance $\leq$10 mL/min or serum creatinine $\geq$8 mg/dl), and deterioration in daily activities. Thereafter the criteria have been used for 20 years. However, the changes in patients' characteristics required the revision of these criteria.

Therefore, a committee for the Ministry of Health and Welfare was organized, and the committee made a new guideline in 1991 (Kawaguchi and Mimura 1991). The guideline was based on the previous criteria and adopts a scoring system shown in Table 1.4. The patients who are diabetic, old, or young were considered to have higher priority for initiating dialysis treatment. The validity of this guideline was confirmed by the committee itself and also by the data from JRDR later. The guideline had been widely used in considering dialysis

Table 1.4 The scoring system adopted in the Japanese guideline in 1991

Factors	Scores
1. Uremic signs and symptoms	
Numbers of observed signs and/or symptoms listed in Table 1.1	
≥ 3	30
2	20
1	10
2. Renal function	
Serum creatinine [mg/dl] (creatinine clearance [mL/min])	
≥ 8 (<10)	30
≥ 5, <8 (≥10, <20)	20
≥ 3, <5 (≥20, <30)	10
3. Disturbance of activities in daily living	
Bedridden due to uremic symptoms	30
Severely disturbed	20
Moderately disturbed and find difficulties in commuting, schooling, or daily works	10
4. Younger (<10 years old), older (≥ 65 years old), or with systemic vasculitis	10

When the summations of each score become 60 or more, the dialysis initiation is considered. Adapted from Kawaguchi and Mimura (1991)

initiation as well as the qualification for beneficiary of medical care for persons with disability.

In 2009 the Japanese Society for Dialysis Therapy (JSDT) published a guideline concerning peritoneal dialysis (the English version was published in 2010) (Working Group Committee for Preparation of Guidelines for Peritoneal Dialysis Japanese Society for Dialysis Therapy, Japanese Society for Dialysis Therapy 2010). In the guideline, they stated the timing of peritoneal dialysis initiation. Initiation of dialysis must be considered in patients with stage 5 CKD (GFR < 15.0 mL/min/1.73 m^2) if they have signs or symptoms of uremia resistant to medical treatment. And also, initiation of dialysis is recommended before GFR reaches 6.0 mL/min/1.73 m^2. This guideline sets higher eGFR target to initiate dialysis, because it was made before publication of the results of IDEAL study, and PD requires more residual renal function than HD does.

As for hemodialysis initiation, another committee was formed within JSDT and published a new guideline on hemodialysis initiation. The Japanese version was published in 2013 and the English version was published in 2015 (Watanabe et al. 2015). This guideline has several specific points. First, the renal function was recommended to be assessed by GFR instead of creatinine values. Second, considerations about signs and symptoms, malnutrition, and deterioration of ADL were emphasized. Third, the GFR values at which consider the dialysis initiation were set 15, 8, and 2. The GFR of 15 mL/min/1.73 m^2 is the value from which dialysis becomes an option of therapies for ESRD. The GFR of 8 mL/min/1.73 m^2 is the value above which the prognosis of the patient is considered worse and until which dialysis therapy might be deferred, if no compelling indications. The GFR of 2 mL/min/1.73 m^2 is the value for initiation of dialysis treatment even if the patients without any uremic symptoms. Forth, the importance of early referral, proper timing of access creation, and comprehensive pre-dialysis management was emphasized. The guideline indicated the flow of consideration about dialysis initiation (Fig. 1.1).

1.4.4 European Best Practice Guidelines (EBPG)

In 2002, the previous version of European Best Practice Guideline (EBPG) was published (European Best Practice Guidelines Expert Group on Hemodialysis ERA 2002). This version told that dialysis should be instituted whenever the GFR is <15 mL/min and there is one or more of the following: symptoms or signs of uremia, inability to control hydration status or blood pressure, or a progressive deterioration in nutritional status. In any case, dialysis should be started before the GFR has fallen to 6 mL/min/1.73 m^2, even without symptoms.

In 2011, the update version after IDEAL study was published (Tattersall et al. 2011). The recommendations in 2002 were not significantly changed, but the absolute eGFR value of 6 mL/min/1.73 m^2 at which dialysis therapy should start was made vaguer. The guideline tells as follows—in patients with a GFR <15 mL/min/1.73 m^2, dialysis should be considered when there is one or more of the following: symptoms or signs of uremia, inability to control hydration status or blood

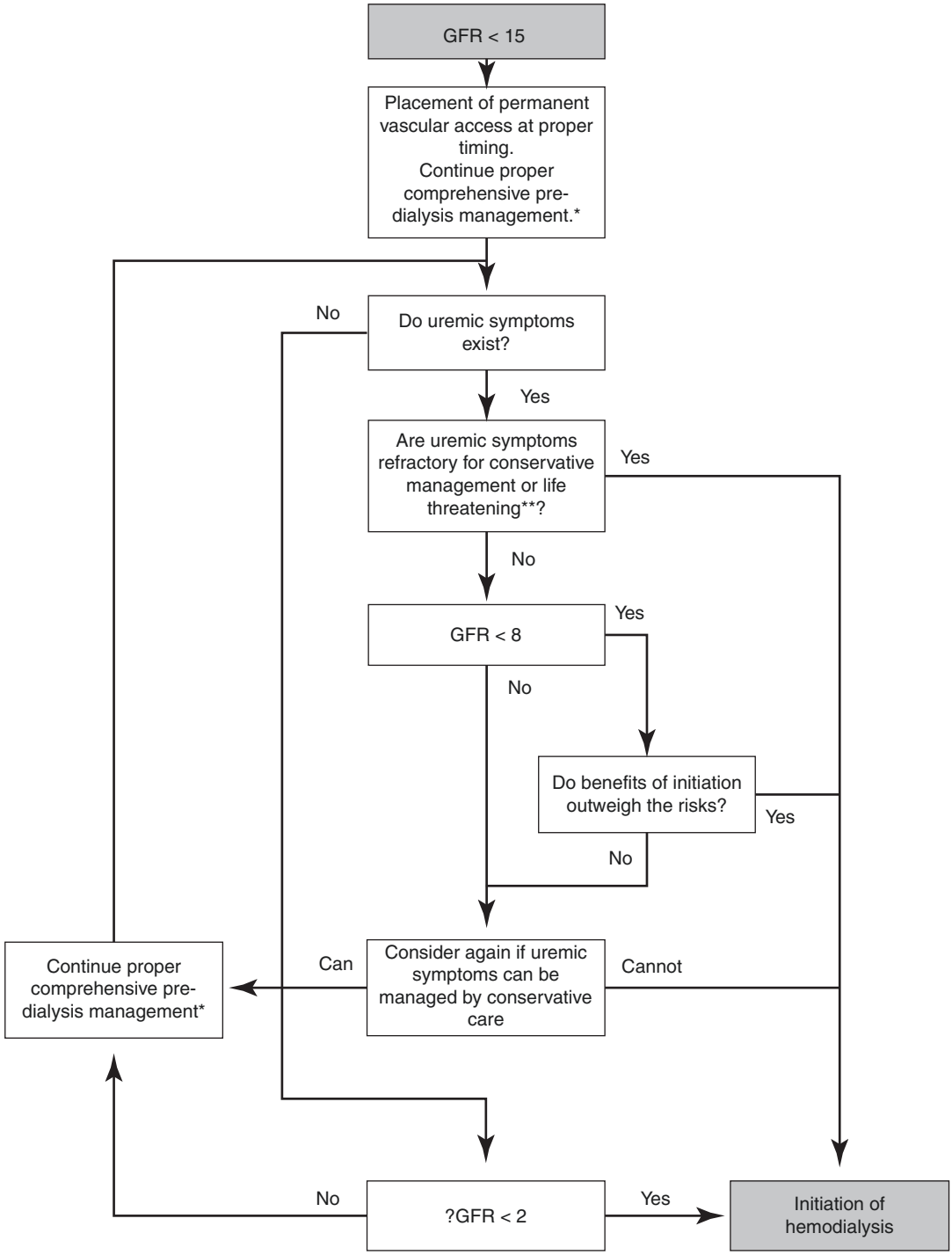

Fig. 1.1 Flow of considering the indication of dialysis initiation described in JSDT guideline in 2013. When the GFR falls below 15 mL/min/1.73 m^2, the option of dialysis can be considered. However, comprehensive pre-dialysis management should be undertaken as long as possible, unless uremic symptoms are refractory for conservative management or life-threatening. Once GFR falls below 8 mL/min/1.73 m^2, initiation of dialysis is considered, when the benefits of initiation outweigh the risks or uremic symptoms cannot be managed conservatively. When GFR falls below 2 mL/min/1.73 m^2, even if the patient is asymptomatic, dialysis should be initiated. Abbreviation: GFR, glomerular filtration rate. Adopted from reference (Watanabe et al. 2015)

pressure, or a progressive deterioration in nutritional status (majority of the patients will be symptomatic in the range 9–6 mL/min/1.73 m^2). In high-risk patients, e.g., diabetics and those whose renal function is deteriorating more rapidly than eGFR 4 mL/min/year, a planned start to dialysis while still asymptomatic may be preferred, if close monitoring is not feasible or if uremic symptoms may be difficult to be detected. Asymptomatic patients presenting with advanced CKD may benefit from a delay in starting dialysis in order to allow preparation, planning, and permanent access creation rather than using temporary access.

1.4.5 Kidney Health Australia Caring for Australasians with Renal Impairment (KHA-CARI Guidelines) (Australia)

Kidney Health Australia Caring for Australasians with Renal Impairment (KHA-CARI) Guidelines also have been published for wide ranges of kidney diseases. The guidelines for dialysis initiation, "Level of renal function at which to initiate dialysis" (The CARI Guidelines 2005b) and "Other criteria for starting dialysis" (The CARI guidelines 2005a), were published online in 2005. In these guidelines, the timing of starting dialysis therapy was recommended both from the GFR levels and signs or symptoms relating uremia.

As for the renal function (The CARI Guidelines 2005b), they set two GFR levels. One is 10 mL/min/1.73 m^2. The patients are commenced dialysis when GFR falls below approximately 10 mL/min/1.73 m^2, if there is evidence of uremia or its complications such as malnutrition. Occasionally, patients may require to initiate dialysis at a higher GFR. The other is 6 mL/min/1.73 m^2. Even if there is no evidence of uremia or its complications including malnutrition, the patients are commenced dialysis when GFR falls below approximately 6 mL/min/1.73 m^2.

As for the signs and symptoms (The CARI guidelines 2005a), the stress was placed on the presence of malnutrition, which is suspected due to uremia and is not responsive to dietary intervention or correction of other reversible causes. The patients are commenced dialysis at first indication of such malnutrition. On the other hand, the existence or appearance of "absolute indications," described below is no longer valid for indications for dialysis initiation, and their presence suggests delayed initiation. In this case, the absolute indicators are pericarditis, fluid overload, and hypertension poorly responsive to non-dialytic treatment, hyperkalemia, acidosis, advanced uremic encephalopathy and/or neuropathy, significant bleeding diathesis, severe nausea, and vomiting. Similarly, traditional "relative indications" may not be useful, because they are largely subjective and may be due to intercurrent diseases. These relative indicators include anorexia, profound fatigue and weakness, impaired cognition, memory and attention span, severe pruritus, depression, and poor interpersonal relationship.

1.4.6 United Kingdom (The Renal Association)

The Renal Association in the United Kingdom has periodically published the guidelines concerning CKD or ESRD. The current version of the guideline about dialysis initiation, "Planning, initiation & withdrawal of Renal Replacement Therapy," was published online in 2014 (Warwick et al. 2014). This guideline covers wide-range of the field including education or referral to nephrologists, initiating RRT, and withdrawal.

In the section about initiation, the guideline recommends that the decision to start RRT in patients with CKD stage 5 (eGFR <15 mL/min/1.73 m^2) should be based on a careful discussion with the patient of the risks and benefits of RRT taking into account the patient's symptoms and signs of renal failure, nutritional status, comorbidity, functional status, and the physical, psychological, and social consequences of starting dialysis in that individual.

Moreover, the guideline underscores RRT starts in a controlled manner, with established permanent access and without hospitalization. Thus, CKD stage 4–5 patients or CKD stage 3 with rapid progression should be referred to a

nephrologist. And most patients with eGFR <30 mL/min/1.73 m^2 and declining should receive timely and personalized information about RRT options. All patients with severe CKD (stage 5 and progressive stage 4) should be offered an education program about CKD and ESRD options with their families or carers. Such multistep approaches are intended for appropriate dialysis initiation.

1.4.7 The Canadian Society of Nephrology

Canadian Society of Nephrology also published the guideline about dialysis initiation, although it was published in 1999 (Churchill et al. 1999). The guideline recommended that symptoms or signs of uremia or evidence of malnutrition should be investigated, when the GFR is less than 12 mL/min. If there is evidence of uremia or if the PNA is less than 0.8 g/kg/d or if there is clinical malnutrition determined by SGA, dialysis initiation is recommended. When the GFR is less than 6 mL/min, dialysis initiation is recommended without symptoms. Above all, the guideline described that all decisions should be based on discussion of the biochemical and nutritional data with the patient and family with the social impact of the decisions into account.

1.5 Pre-dialysis Care

The significance of pre-dialysis care, especially by multidisciplinary team, has been demonstrated. An Italian study investigated the efficacy of these multidisciplinary teams of doctor, nurse, and dietician on the CKD stage 5 patients. Patients' age was the median of 72 years old, 19% of the population was diabetic, and eGFR was 9.5 mL/min/1.73 m^2 at baseline. Among them 62% of the population started dialysis at their eGFR of 6.1 ± 1.9 mL/min/1.73 m^2 after 13.9 ± 15.6 months. Moreover, the patients with eGFR lower than median (5.7 mL/min/1.73 m^2) experienced better survival after initiation (Dattolo et al. 2015). Such multidisciplinary care also reportedly reduces the medical costs during the first 6 months of dialysis (Yu et al. 2014). Another study demonstrated that dietitian care more than 12 months before initiation of dialysis was associated with better 1-year survival after start of dialysis (Slinin et al. 2011).

As well as the timing of dialysis initiation itself, the timing when the patients were referred to nephrologist is also important for the prognosis after start of dialysis.

Many studies have investigated the timing of referral and subsequent clinical outcomes by comparing two groups, i.e., early referral and late referral groups. Most of them studied the timings in terms of survival after initiation of dialysis, while some others also investigated other comorbidities such as infection, hospitalization, or anemia management. In general, early referral was shown to be associated with better clinical outcomes. However, most importantly, the definitions of early and late referral were diverse, and conclusive timing of early referral might be difficult to be made.

Hasegawa et al. investigated the frequency, and the timing of pre-dialysis nephrology visits was associated with the 1-year survival after dialysis initiation. The patients who had more chance to receive nephrology clinics experienced better survival thereafter (Hasegawa et al. 2009).

Other meta-analysis investigated the timing of referral and its consequences on clinical outcomes including 63,887 patients from 40 cohort studies. The study found that early referral was significantly associated with reduced 3-month mortality, hospitalization periods, and catheter use for vascular access. Improved blood pressure control and higher proportion of ESA use were found in the early referral group (Smart et al. 2014).

What makes the early referral better in clinical outcomes? Mendelssohn et al. investigated this point. They studied the relationship between the timing of referral and survival by the groups with or without vascular access at the initiation of dialysis therapy. They found that the patients with vascular access and referred early exhibited the best survival, while the patients referred early but without vascular access demonstrated similar survival to the patients who were

referred late (Mendelssohn et al. 2011). Another study indicated the efficacy of predialysis education program. The program includes explanations of RRT, preparation of access placement, and referral to surgeons who will create an access. The patients who received such program experienced higher rate of existence of vascular access and better 90-day survival after initiation of dialysis treatment (Lacson et al. 2011). The fact indicated that the advantage of early referral might derive from the early creation of vascular access and avoidance of temporary vascular access which may relate to worse outcomes.

However, there are several barriers for these appropriate early referral or optimal dialysis initiation. From England National Health Service database, an important finding was obtained. In the study, the late referral was defined as referral to nephrologist less than 90 days prior to the initiation of dialysis, and the proportion of such patients was high and about 34% of total population. Moreover, 49% of those who were referred late experienced some medical contacts log before the referral. Thus appropriate monitoring renal function at such occasions might have led to the referral at more appropriate timing (Blunt et al. 2015). Another issue is suboptimal initiation of dialysis might occur after referral to the nephrologists. Hugh et al. demonstrated that 56.4% of patients started dialysis suboptimally, and 65% of them were not attempted to create permanent vascular access before initiation even among the patients who referred to nephrologist for more than 12 months (Hughes et al. 2013). Similarly, Al-Jaishi et al. demonstrated that only 39% of non-late referral (nephrologist referral ≥3 months of initiation) patients had been created permanent access before dialysis initiation (Al-Jaishi et al. 2015). The former study investigated the reasons for these delays. It demonstrated that the reasons were patient-related delays 31%, acute on CKD 31%, surgical delay 16%, and late decision-making 11% (Hughes et al. 2013). We should be aware of these factors among early referral patients and make sure to take a proper pathway to dialysis initiation.

1.5.1 Vascular Access Existence of Initiation of Dialysis

Above mentioned, proper permanent vascular access placement relates to better survival after initiation of dialysis treatment not only in shorter period of time (Chesser and Baker 1999) but also in longer period of time (Lorenzo et al. 2004). The former study demonstrated the existence of permanent vascular access related to better survival during 90 days after initiation of dialysis treatment (Chesser and Baker 1999), while the latter indicated that patients with arteriovenous fistula exhibited better outcome of 1 and 2-year survival after dialysis initiation (Lorenzo et al. 2004). Such relationship does not only apply to the younger generation. Kawanishi et al. demonstrated that catheter use was more prevalent among the older population. Even such older population as ≥70 years old experienced worse adverse outcome compared to arteriovenous fistula (AVF) or arteriovenous graft (AVG) (Kawanishi et al. 2015). Besides clinical outcomes, economic benefits are also demonstrated. The patients who were created vascular access after dialysis initiation experienced higher medical costs and longer hospitalization periods than those with vascular access at the time of initiation (Wu et al. 2009).

A recent study demonstrated an interesting result that the patients with advance CKD who were created vascular access experienced slower decline of renal functions (Sumida et al. 2016). The authors concluded that such favorable effects may be due to patients' improved adherence, intensified nephrologist care, or other physiological mechanism to be investigated. On the other hand, there is a conflicting result that the patients who created vascular access during stage 4 of CKD exhibited the worse survival compared to others (Hiremath et al. 2011).

DOPPS data investigated the timing of first cannulation of vascular access after creation from the view point of subsequent access survival (Rayner et al. 2003). The study indicated that the incidence of access failure was significantly higher, if the first cannulation was made within 14 days after creation. Recently, Hod et al. investigated the time period from creation of AVF to

dialysis initiation retrospectively among older patients in USRDS database. They found that the AVF success rate (dialysis initiation with AVF initially placed) increased with the periods longer. They concluded that dialysis initiation at 6–9 months after creation of AVF experienced the highest AVF success rate, although the mean number of procedures for access intervention per patients became also higher at this time (Oliver et al. 2012).

Above all, the timely placement of proper vascular access requires adequate pre-dialysis nephrologist care.

1.6 Post-dialysis Initiation Management

1.6.1 Early Mortality

Several studies have demonstrated that the early mortality is high among dialysis population. Chan et al. investigated the mortality and hospitalization during the first 90 days of dialysis among more than 300,000 incident patients in the United States (Chan et al. 2011). They found that the relative risks of death and hospitalization during the first 2 weeks were 2.72 (95%CI 2.50–2.94) and 1.95 (95%CI 1.92–2.01), respectively, compared to those of the patients who survived the first 1 year. Age (>65 years old), catheter use for vascular access, higher comorbid conditions, and lower serum albumin were major factors that related with higher mortality within the first 2 weeks. DOPPS demonstrated that the mortality soon after initiation up to 120 days was high, especially among older (≥ 65 years old) patients (Robinson et al. 2014). Similar results were obtained from other studies (Saggi et al. 2012; Lukowsky et al. 2012). One of them indicated that inadequate preparation of the patients for dialysis treatment was related to higher mortality during these transitional periods (Saggi et al. 2012). Therefore, the early referral to nephrologists and proper pre-dialysis care with multidisciplinary teams are again warranted to improve the early survival among the dialysis patients.

1.6.2 Importance of Pre-dialytic Care and Conservative Management

The numbers of older dialysis patients are rapidly growing especially in developed countries. It is often possible that these patients cannot enjoy the survival benefits from initiation of dialysis treatment. Therefore, conservative management for far advanced CKD has become the topics of debate recently. Several studies compared the survival between conservative management and dialysis initiation and found that the patients with very elderly (usually more than 80 years old) and/or with many comorbidities experience comparable survival between these two therapies (Williams 2012; Verberne et al. 2016). A meta-analysis compared these two modalities on 13 studies (O'Connor and Kumar 2012). They found that even the patients who were implemented conservative management survived at least 6 months (range 6.3 to 23.4 months). Although the survival benefit of dialysis decreased with comorbidities, the patients managed conservatively experienced a high symptom burden to require further palliative cares (O'Connor and Kumar 2012).

For more practical approach, the delay of initiation of dialysis treatment with multidisciplinary teams and close monitoring, especially appropriate dietary therapies, have been proposed. Brunori et al. from Italy demonstrated importance of pre-dialysis nephrology care on advanced CKD patients. They recruited old CKD patients (more than 70 years old) without dialysis, and their eGFRs were between 5 and 7 mL/min/1.73 m^2. They allocated the patients into two groups; one received dialysis therapy soon after allocation, while the other received intensive pre-dialysis care including very low-protein diet with supplementation of keto acids and essential amino acids. The patients allocated the dietary management group could defer their dialysis treatment by the median period of 10.7 months. Moreover, the survival between the two groups was comparable, and the dietary group exhibited even better survival by per protocol analysis after adjustment of baseline unbalances (Brunori et al.

2007). This result indicates the possibility that pre-dialysis care for far advanced CKD patients provided with supplemented very low-protein diet and close monitoring could safely retard dialysis initiation. Thus the patients can enjoy the period free from dialysis treatment and can receive moratorium during which preparation for dialysis treatment can be made such as proper access creation or selection of the most appropriate modality.

1.6.3 Incremental Dialysis

We discussed the timing of dialysis initiation above and the controversy on it. A concept has been proposed since late 1990s about gradual increase in dialysis dose after initiation of dialysis. At first, this method was applied to peritoneal dialysis patients who had still enough residual renal function and did not require full dose of peritoneal dialysis (Burkart 1998; Golper 1998). It is described that advantages of this approach were reduced medical costs, glucose exposure, protein loss, membrane fatigue, and greater patient acceptance. However, the close monitoring of residual renal function, frequent prescription changes, potentially reduced removal of middle molecules, and uncertainty about clinical outcomes were considered its disadvantages (The CARI guidelines 2005c).

On the other hand, the efficacy of less frequent hemodialysis at the initiation on the patients with sufficient residual renal functions has been investigated. Recently, Obi et al. demonstrated the association of twice-weekly hemodialysis and preservation of residual renal function (Obi et al. 2016). Many studies have demonstrated that preservation of residual renal function related to better survival among hemodialysis patients (Wang and Lai 2006; Vilar et al. 2009) as well as peritoneal dialysis patients (Shemin et al. 2000; Termorshuizen et al. 2003). Another investigator group also demonstrated the similar results. They combined incremental dialysis and supplemented very low-protein diet and found that the patients who received such incremental dialysis therapy experienced better preservation of residual renal function, reduced accumulation of uremic solute, and less hospitalization compared to the patients in control group (Caria et al. 2014). Therefore, incremental hemodialysis for the incident hemodialysis patients at lower frequency might potentially offer clinical benefits. However, no randomized control trials have been performed to compare incremental dialysis and conventional thrice-weekly hemodialysis treatment. Therefore, there remains the possibility of selection or survival biases that patients with much residual renal function remained incremental dialysis. Kalantar-zadeh et al. publicized and proposed criteria for incremental dialysis (Table 1.5) (Kalantar-Zadeh et al. 2014). Above all, future randomized control trials are required to compare incremental dialysis with or without dietary protein restriction and conventional thrice-weekly hemodialysis in terms of hard outcomes such as survival or cause-specific mortality as well as preservation of residual renal function. The results will provide concrete evidences about such infrequent hemodialysis at the initiation.

Table 1.5 Treatment criteria for twice-weekly HD

1.	Good RKF with urine output >0.5 L/d
2.	Limited fluid retention between two consecutive HD treatments with fluid gain <2.5 kg (or <5% of ideal dry weight) without HD for 3–4 d
3.	Limited or readily manageable cardiovascular or pulmonary symptoms without clinically significant fluid overload
4.	Suitable body size relative to RKF; patients with larger body size may be suitable for 2x/wk. HD if not hypercatabolic
5.	Hyperkalemia (K > 5.5 mEq/L) is infrequent or readily manageable
6.	Hyperphosphatemia (P > 5.5 mg/dL) is infrequent or readily manageable
7.	Good nutritional status without florid hypercatabolic state
8.	Lack of profound anemia (Hb > 8 g/dL) and appropriate responsiveness to anemia therapy
9.	Infrequent hospitalization and easily manageable comorbid conditions
10.	Satisfactory health-related quality of life

Lack of systolic dysfunction (ejection fraction >40%) and no major coronary intervention over the previous 3 months. *Hb* hemoglobin, *HD* hemodialysis, *K* potassium, *P* phosphorus, *RKF* residual kidney function

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