When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study

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Scope of the position statement

This position statement is intended to be used in conjunction with the original 2002 European guideline on when to start dialysis [1]. The original guideline was based on a formal review of all evidence available at the time. The position statement considers mainly the results of the Initiating Dialysis Early and Late (IDEAL) study [2], but it also considers other relevant studies published since 2002. A formal literature review was not undertaken. The position statement has been prepared by a working group whose members were nominated by the European Renal Best Practice (ERBP) advisory board.

Introduction

The original guideline on when to start dialysis [1], published in 2002 states:

Guideline I.3

(1) Dialysis should be instituted whenever the glomerular filtration rate (GFR) is <15 mL/min and there is one or more of the following: symptoms or signs of uraemia, 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/1.73m^2, even if optimal pre-dialysis care has been provided and there are no symptoms.

(2) High-risk patients e.g. diabetics may benefit from an earlier start. (Evidence level: C)

(3) To ensure that dialysis is started before the GFR is 6 mL/min, clinics should aim to start at 8–10 mL/min. (Evidence level: C)

The guideline on measurement of renal function [1] states:

Guideline I.1.1

Renal function should not be estimated from measurements of blood urea or creatinine alone. Cockcroft and Gault equation or reciprocal creatinine plots should not be used when the GFR is <30 mL/min or to determine the need for dialysis.

Guideline I.1.3

(1) GFR should only be estimated using a method, which has been validated in patients with advanced renal failure. The preferred method for calculating GFR in advanced renal failure is the mean of urea and creatinine clearance (CC). The latter is best calculated from a 24-h urine collection and normalized to 1.73m^2. (Evidence level: C)

(2) Other examples of validated GFR estimations are: Modifation of Diet in Renal Disease (MDRD) equation, indicator decay methods (e.g. iohexol, iothalamate, ethylenediamine tetraacetic acid, inulin), CC after oral cimetidine. (Evidence level: C)

The original 2002 guideline on when to start dialysis was graded Level C, using the grading system in use at that time, meaning based on opinion. However, the use of the word 'should' indicates that it is a strong recommendation, though based on very low evidence (1D, using current grading).

At the time the 2002 guideline was being prepared, dialysis tended to be started with an estimated glomerular filtration rate (eGFR) of ~6 mL/min [3] and there was an

impression that dialysis was started too late in many cases. In the years following the publication of the guideline, there has been a tendency for dialysis to be started at higher levels of renal function. Recent studies have, however, suggested that this trend could be counterproductive [4].

The IDEAL study

The original authors of the 2002 guideline believed that there would never be any randomized controlled trial (RCT) on when to start dialysis. The following text appears in the commentary which forms part of the guideline: 'there is clearly a need for a prospective, randomized controlled study to clarify this issue. It is recognized that such a study would be very difficult to perform, as it would be almost impossible to enforce an unbiased subject allocation process'. Those responsible for the design and conduct of the IDEAL study are to be congratulated for overcoming these difficulties and providing us with the required RCT evidence.

The IDEAL study enrolled patients >18 years old with CC between 10 and 15 mL/min/1.73m^2. Patients were randomized to two groups, named 'early' and 'late'. The early group were planned to start dialysis when CC was 10–14 mL/min/1.73m^2 and the late group at 5–7 mL/min/1.73m^2. The study protocol allowed patients in either group to start dialysis based on clinical indications, regardless of CC, if that was deemed necessary by the patient's nephrologist.

CC was calculated using the Cockcroft and Gault equation [5], multiplied by 1.73 and divided by surface area calculated using the Dubois and Dubois equation [6]. Mean follow-up was 3.64 and 3.57 years in the early and late groups. There were 404 and 424 patients in the early and late groups, respectively.

The results of the IDEAL study showed no difference in mortality between the early and late groups. Seventy-six per cent of the patients in the late group started dialysis with CC higher than the intended 7 mL/min/1.73m^2, the majority due to uraemic symptoms. The average CC at the time of starting dialysis was 12.0 and 9.8 mL/min/1.73m^2 in the early and late groups, respectively. Yet, the late group started dialysis on average 6 months later than the early group.

The average body mass index (BMI) and albumin of the IDEAL study participants was 29 kg/m^2 and 38.4 g/L. This compares with BMI 24.9 kg/m^2 and albumin 37.5 g/L in the contemporary Netherlands cooperative study in the adequacy of dialysis (NECOSAD) [3] study on Dutch dialysis patients. Only 4 and 8% of the IDEAL, early and late group required temporary lines as the dialysis access. The dialysis outcomes and practice patterns study demonstrated that ~45% of patients start dialysis with temporary access [7]. Sixty per cent of the IDEAL study patients started dialysis with peritoneal dialysis as the initial modality, compared to 20% according to the european registry [8]. Therefore, the IDEAL study participants could be considered particularly well prepared and well nourished, compared to typical European dialysis patients.

Renal function was retrospectively calculated as eGFR using the MDRD method [9]. The mean eGFR on starting dialysis in the early and late groups was 9.0 and 7.2 mL/min/1.73m^2.

Other studies published since 2002

Six recent observational studies, published since 2002, have compared outcomes in patients starting dialysis at various levels of eGFR. These studies included large numbers of patients, in some cases >100 000, in registry-type data sets, including the United States Renal Data System (USRDS) [10,11], Bureau of National Health Insurance in Taiwan [12], European Registry [13], Renal Epidemiology and Information Network French Registry [14] and the Canadian Organ Replacement Registry [15]. These studies all demonstrated a progressively reduced mortality with starting dialysis at lower levels of eGFR. The results of these studies were in agreement with an earlier study from the USRDS [16] which was taken into consideration in the 2002 guideline. These studies provide convincing and reproducible evidence that there is an association between high eGFR when dialysis starts and increased mortality. They provide some evidence that starting dialysis early could be harmful. As observational studies, they do not prove that starting dialysis with higher eGFR causes the worse outcome, though this is a possible explanation for the results. There are other possible explanations for the association:

- Patients with low muscle mass due to inactivity or malnutrition will have a lower creatinine generation rate. Patients with fluid overload will dilute their serum creatinine. Both groups will have higher co-morbidity, yet have lower serum creatinine. Since eGFR is calculated from serum creatinine, eGFR will be overestimated in these patients and they are more likely to be included in 'earlier' start groups [17].

- Patients with symptoms or co-morbidity are more likely to be started on dialysis early. Multivariate adjustment for co-morbidity indeed decreased the benefit of starting with low eGFR, but it did not disappear [10–13].

- Patients were only included in the study if they actually started dialysis. Patients dying before dialysis started (possibly due to uraemia) were excluded. Only the fittest patients survive long enough to be included in the late start groups. In the Huang [12] study, deaths within the first 90 days of starting dialysis were excluded, further enhancing this 'survivor bias'

On the other hand, these studies are prone to the 'lead time bias', where the extra period of life gained by delaying dialysis is not taken into account. This will bias the results in favour of early start [3,18].

A Swedish study, based on a complete nationwide inception cohort of chronic kidney disease (CKD) stage 4–5 patients (as part of a nationwide case–control study of risk factors for CKD) followed up for 5 years has recently been completed [19]. This study avoided the lead time and survivor bias by enrolling patients prospectively when their GFR dropped <16 mL/min/1.73m^2. The study was observational, and so was subject to the other causes of bias. The

study results agreed with the other observational studies: mortality was higher in patients starting dialysis with higher eGFR.

The earlier study by Traynor *et al.* [18] attempted to correct for the lead time bias retrospectively by accounting survival from the time when CC (by Cockcroft and Gault method) dropped <20 mL/min rather than from the time dialysis started. This study did not show any significant difference between early and late start. A non-significant benefit for early start was eliminated by the lead time bias correction. Unlike the Swedish study [19], Traynor's study only included patients who eventually started dialysis so was subject to the survivor bias.

Depending on how the potential causes of bias are accounted, these observational studies could be interpreted as evidence in favour of delaying dialysis as much as possible. The studies did not indicate a lower limit for eGFR, below which further delay could be counterproductive; though logic dictates that there must be (otherwise dialysis would never be required).

However, the results that are interpreted in these studies suggest that renal function based on serum creatinine (as with eGFR) is useless or even misleading as a guide on when to start dialysis. The wide range of eGFR when dialysis starts suggests that either nephrologists are ignoring eGFR in planning the start to dialysis, that eGFR does not represent renal function very well or that patients have widely differing tolerance to uraemia.

One of the papers analysing, the NECOSAD study [3] was one of the few studies comparing GFR before dialysis started and subsequent outcome and where GFR was calculated from timed urine collections (as the mean of urea and CC) rather than calculated from serum creatinine. Unlike the other observational studies, the confounding effects of malnutrition, dilution and low muscle mass on serum creatinine did not affect the assessment of renal function. The NECOSAD study showed a slightly improved survival with higher GFR at the start of dialysis. In this respect, the NECOSAD study agreed with the results of the earlier Canada—USA (CANUSA) study [20], where renal function was also assessed from urine collections, though these were performed shortly after the start of dialysis. Both NECOSAD and CANUSA were subject to the lead time bias. The NECOSAD study investigators suggested that, if lead time bias was taken into account, it would remove or reverse this benefit of early start [3].

The NECOSAD study showed a strong association between nutritional indices and GFR in the period before dialysis starts [3]. There was a tendency for normalised protein nitrogen appearance to drop <0.8 g/kg/day (the limit of malnutrition) as GFR drops <5 mL/min/m^2.

Two further studies have shown that renal function measured some months after starting dialysis are powerfully associated with reduced mortality, even if dialysis dose is reduced [21,22]. Higher GFR, some months after starting dialysis could be due to better preservation of GFR after starting dialysis (maybe due to less aggressive kidney disease), not necessarily due to starting dialysis with higher GFR. These observational studies may not provide strong evidence to support earlier dialysis start but do suggest that

measured renal function should be taken into account in any future dialysis outcome study.

As an RCT, the IDEAL study was designed to eliminate the various causes of bias which are unavoidable in observational studies.

Interpretation of the IDEAL study results

The IDEAL study did not establish the safety of delaying dialysis until eGFR drops <7 mL/min/1.73m^2 as 76% of patients allocated to the late group actually started with higher CC due to symptoms. Even in the early start group, there were patients who were started due to uraemia or fluid overload. It is possible that mortality would have been higher in the late group if dialysis had been delayed until CC had dropped to 7 mL/min/1.73m^2 in the symptomatic majority.

The IDEAL study provides evidence that the majority of patients develop symptoms when CC is >7 (=MDRD eGFR >6) mL/min/1.73m^2.

The IDEAL study has shown that there is no disadvantage in ignoring CC and starting dialysis based on symptoms, at least in groups comparable to the IDEAL study participants and when dialysis is started anyway when CC is 5–7 mL/min/1.73m^2. Compared to starting dialysis with CC of 10–14 mL/min/1.73m^2 (i.e. pre-emptive in the absence of symptoms), waiting for symptoms or CC 5–7 mL/min/1.73m^2 gained a 6 months delay before starting dialysis.

Method of assessing kidney function

The IDEAL study used estimated CC based on serum creatinine, as calculated by the Cockcroft and Gault method and corrected for surface area. This is closely related to the more commonly used MDRD method for estimating eGFR from serum creatinine (though the MDRD method does not require a separate surface area correction step). The IDEAL study demonstrated that CC, calculated by Cockcroft and Gault was ~35% higher than GFR, calculated by the MDRD method.

The IDEAL study demonstrates that, in this range of CC, serum creatinine, and thus also the clearances estimated from it, is not a reliable marker of kidney function or at least of uraemic toxicity.

A later analysis of the NECOSAD study compared methods of estimating GFR just before the start of dialysis [23]. GFR estimated as the mean of urea and CC in timed urine collections (mGFR) did not agree with GFR estimated from serum creatinine using the MDRD equation. In agreement with other studies, higher eGFR was associated with higher mortality rates. On the other hand, mGFR was not associated with mortality rate. The difference between mGFR and eGFR in this study was shown to be related to muscle mass (which was calculated independently to serum creatinine). The eGFR was related to muscle mass, the higher the muscle mass, the higher the serum creatinine and the lower the eGFR. There was no association between muscle mass and mGFR.

Estimated clearances should, thus, not be used to guide decisions on when to start dialysis. Whether other methods to estimate renal clearance, such as iohexol clearance, mean of urea and CC from timed urine collection, serum cystatin C, or tracer studies, perform better to provide a more solid basis besides clinical observation to base these decisions, cannot be answered so far.

Applicability of the IDEAL study to routine clinical practice

The IDEAL study participants were well prepared for dialysis and well nourished compared to typical European dialysis patients. The nature of a clinical trial makes it likely that they were more closely supervised compared to usual clinical practice.

Delaying dialysis until there are symptoms would carry a risk of harm or death due to uraemia. In the IDEAL study, this risk was negligible. In normal clinical practice supervision may be less tight, and this risk may be greater [24]. It could outweigh any benefit to the patient by delaying dialysis. The risk would be increased in patients whose renal function is declining rapidly, who are unreliable clinic attenders, have cognitive impairment or whose clinical supervision cannot be guaranteed for any reason.

The IDEAL study provides further evidence that the decision on when to start dialysis is difficult and cannot be guided by any single objective measurement. It makes sense that these decisions are made by experienced staff in a dedicated pre-dialysis clinic. The cost of establishing the clinic would tend to be offset by potential savings resulting from delaying dialysis in selected patients and by avoiding the cost of unplanned or poorly-prepared dialysis starts. In general, it should be cheaper and more satisfactory for a patient to be followed up in a dedicated pre-dialysis clinic.

Updated guidance

The 2002 guidance is not significantly changed. The evidence levels are increased by the studies published since 2002. The caution against using creatinine and CC to guide dialysis start is strengthened. A caution that eGFR calculated by the MDRD method is not useful in determining need for dialysis has been added. The emphasis on using GFR of 6 mL/min/1.73m^2 as an absolute lower limit to starting dialysis is made more vague. Support for establishing advanced CKD, clinics has been added.

Guideline I.3

(1) Patients with advanced CKD should be prepared for dialysis, kidney transplant or conservative care before their CKD becomes symptomatic. For patients who are expected to require dialysis, this includes advance preparation of appropriate access. This process also includes careful observation for signs and symptoms of uraemia and should, ideally, be started while GFR is >15 mL/min/1.73m^2. Supervision in a dedicated clinic for patients with advanced CKD is recommended (1C, Strong recommendation based on low-quality evidence).

(2) In patients with a GFR <15 mL/min/1.73m^2, dialysis should be considered when there is one or more of the following: symptoms or signs of uraemia, inability to control hydration status or blood pressure or a progressive deterioration in nutritional status. It should be taken into account that the majority of patients will be symptomatic and need to start dialysis with GFR in the range 9–6 mL/min/1.73m^2 (1A Strong recommendation based on high-quality evidence).

(3) High-risk patients e.g. diabetics and those whose renal function is deteriorating more rapidly than eGFR 4 mL/min/year require particularly close supervision. Where close supervision is not feasible and in patients whose uraemic symptoms may be difficult to detect, a planned start to dialysis while still asymptomatic may be preferred (1C Strong recommendation based on low-quality evidence).

(4) 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 (2C Weak recommendation based on low-quality evidence).

Guideline I.1.1

Renal function should not be estimated from measurements of blood urea or creatinine alone. Cockcroft and Gault equation or reciprocal creatinine plots should not be used when the GFR is <30 mL/min/1.73m^2 or to determine the need for dialysis. The MDRD-eGFR is useful in identifying CKD and estimating rate of progression but should not be used to determine the need for dialysis or to estimate renal function in Stage 5 CKD (GFR < 15 mL/min/1.73m^2) (1A Strong recommendation based on high-quality evidence).

Need for further research

The observational studies have shown that dialysis is started at a wide range of eGFR, therefore, nephrologists are using other criteria to decide when to start dialysis. These other criteria have not been well defined in the literature. We need observation studies on the criteria used to start dialysis and the association between these criteria and subsequent outcome.

We currently lack any validated and objective measurement of the uraemic state which could be used to guide the decision on when to start dialysis. Even accurately measured GFR has not been tested for this purpose in an RCT. It may be that a composite 'uraemia' score would be required. Any future RCT on dialysis outcome should include measurements of renal function, rather than estimation from serum creatinine.

Dialysis results in relatively less benefit (in terms of physical function and survival) in high risk and elderly patients [25]. These patients are more likely to be started on

dialysis early. This group of patients deserves more study to help us decide on when conservative care would be more appropriate.

Disclaimer. The present text is based upon the information available to the work group at the moment of the preparation of this publication. It has been designed to provide information and assist decision making, but is not intended to define a standard of care or to improve an exclusive course of diagnosis, prevention or treatment. Individual decision making is essential in the approach to any disease and thus also to the start of dialysis in CKD. Variations in practice are inevitable when physicians take into account individual patient needs, available resources and limitations specific for a geographic area, country, institution or type of practice. In addition, evidence may change over time as new information becomes available, so that practice may be modified subsequently. Every practitioner using this text is responsible for its application to any particular clinical situation. The work group members involved in the development of the present text have disclosed all actual and potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional or business interest.

Conflict of interest statement. None declared.

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