The timing of the start of dialysis in elderly patients is driven by the desire to optimize the quantity and quality of life. Limited data exist on how the level of renal function, and uraemic signs and symptoms can be used to determine when dialysis should be initiated in elderly patients. EQUAL, an international prospective cohort study, aims to address these issues. To this end, it will enrol 3500 patients >65 years of age with CKD of various aetiologies under the care of nephrologists. These patients will be followed until death, discharge from the nephrology clinic to primary care or until the end of the observation period after 4 years of follow-up. At the time of enrolment, patients must have an estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73 m² or lower, but should not yet be on dialysis. Standardized data collection will include demographics, lifestyle, comorbidities, uraemic signs and symptoms, nutritional status, medication and routine blood and urine biochemistry. It will also comprise quality of life data, information on decision making including patients preferences and patients satisfaction.

Introduction

Since the 1960s when the first patients began chronic dialysis, the average end-stage renal disease (ESRD) patient has changed from a relatively young patient with glomerulonephritis or polycystic kidney disease into an elderly person with diabetes mellitus or hypertension as cause of renal failure and multiple comorbidities. The increased availability of dialysis as well as the ageing of the general population has contributed to the huge increase in the number of dialysis patients over this period. This growth has had a substantial economic impact given the high costs of dialysis.

Dialysis therapy aims to prolong life and improve the quality of life for patients with ESRD, but mortality rates remain high, especially in elderly patients—58% of elderly nursing home residents die in their first year of treatment [1]. This means that nowadays, at least in specific groups of patients on dialysis, mortality is importantly higher than in patients suffering from common malignancies. These developments, together with the tendency of nephrologists in recent years to start dialysis earlier in the course of disease [2, 3] to try and improve survival on dialysis, have led to an increasing debate on when to start dialysis in terms of renal function and in terms of signs and symptoms. Furthermore, there is substantial discussion concerning the process of decision making by nephrologists and patients, especially if these decisions are regarding elderly patients. The international EQUAL study intends to address these issues. This review provides details on the study’s background and gives a short summary of its design.

The timing of the start of dialysis

Estimated glomerular filtration rate

Usually, dialysis is started at an estimated glomerular filtration rate (eGFR) of 5 to 15 mL/min/1.73 m² [3–7]. As a consequence, the variation in the start of dialysis in terms of eGFR is substantial. Over the past decades, there has been a trend to start dialysis at higher levels of residual renal function [2, 3, 5, 8, 9], also in patients who have relatively few symptoms and signs, to make a so-called ‘healthy start’ on dialysis with positive effects on renal function and nutritional parameters. For example, using the United States Renal Data System (USRDS) data, Rosansky et al. showed that from 1996 to 2005 the percentage of US patients starting dialysis with an eGFR
of >10 mL/min/1.73 m² has more than doubled from 19 to 45% [3]. Furthermore, O’Hare et al. recently showed that, after accounting for changes in the characteristics of new US dialysis patients, from 1997 to 2007 chronic dialysis was initiated on average 147 days earlier. In patients >75 years of age the initiation of dialysis was even 233 days earlier [2].

Several studies have investigated whether there were differences in mortality risk between the start of dialysis at higher levels of eGFR versus the start of dialysis at lower levels of eGFR. Although not anticipated, most observational studies have shown a decreased survival of patients who started dialysis at higher levels of eGFR [4, 6, 9–15] instead of improved survival in these ‘early starters’. The association between the start of dialysis at higher eGFR levels and lower patient survival has been found in both haemodialysis and peritoneal dialysis. Confounding factors may play an important role, as the data of Lassalle et al. suggest that after adjustment for prognostic factors an effect of starting at higher levels of eGFR is absent in patients in whom the start of peritoneal dialysis was ‘planned’ [6]. In addition, many of these studies suffered from methodological shortcomings including lead-time bias and selection bias [16].

A recent randomized controlled trial, the IDEAL study, failed to show a benefit in survival between strategies of starting dialysis at higher levels of eGFR versus starting dialysis at lower levels of eGFR (hazard ratio for the early-start group: 1.04; 95% CI, 0.83–1.30; P = 0.75) [7]. However, the relatively small difference in initial eGFR at which patients actually started dialysis in this study (mean eGFR according to Cockcroft–Gault: 12.0 mL/min versus 9.8 mL/min in the early- and late-start group respectively) may have contributed to the lack of difference in patient survival. From the available evidence, therefore, the level of kidney function at which patient survival and quality of life are improved by starting dialysis remains unknown [17] and the possibility that harm may be done by starting dialysis at higher levels of eGFR cannot be excluded [9, 13]. The mechanisms proposed for the potential harm induced by starting haemodialysis at higher levels of renal function include the more rapid loss of endogenous renal function and the clinically significant hypotension induced by this treatment as shown by Jansen et al. [18]. Furthermore, the recurrent episodes of myocardial ischaemia and ‘stunning’ as demonstrated by McIntyre may be contributory [19].

We therefore support the conclusion of O’Hare et al. that, in the absence of strong evidence of benefit from earlier initiation of chronic dialysis, the trend to start dialysis earlier in the process of deterioration of renal function calls for a careful evaluation of contemporary dialysis initiation practices [2]. As EQUAL investigators we would also like to stress the importance of studying the link between contemporary dialysis initiation practices and patient prognosis.

Uræmic signs and symptoms

Knowledge of the development of uræmic signs and symptoms during the progression of chronic kidney disease (CKD) towards the start of dialysis is limited. Both the IDEAL study and some observational studies confirmed previous data showing that in starting dialysis for ESRD nephrologists consider such signs and symptoms at least as important as the level of residual renal function [7, 20–22]. For example in the late-start group of the IDEAL study, 76% of the patients started dialysis earlier than planned, mainly because of uræmia. A similar variation in the timing of start of dialysis as shown for the eGFR may exist for the presence and severity of signs and symptoms of uræmia. To the best of our knowledge, data on the variation in signs and symptoms at the start of dialysis, on their relative importance for the decision to start dialysis as well as on their association with patient prognosis are lacking. Studies in this area are therefore needed.

Measuring renal function

The counterintuitive results from the observational studies investigating the relationship between the eGFR at the start of dialysis and patient survival and the negative IDEAL trial have raised considerable doubts as to whether the eGFR is suitable as an indicator of renal function in this very low range of renal function when the decision to start dialysis is made. The eGFR based on the modification of diet in renal disease (MDRD) equation and other serum creatinine-based measures of renal function have been shown to be inaccurate and imprecise indicators of residual renal function and to have a different association with patient survival than the measured GFR [20, 23, 24]. Some of the apparent adverse effects of starting dialysis at higher eGFR levels may be due to the dependency of the eGFR on muscle mass [24]. On the other hand, the most valid methods to measure renal function in advanced CKD in routine clinical practice are not known. This leaves us with the problem of not knowing which measure of residual renal function can be used to determine the best moment to start dialysis in relation to patient outcomes.

Preferences of patients and caregivers regarding the decision on when to start dialysis

Qualitative studies about medical decision making on when and whether to start dialysis from the perspective of patients and carers are extremely scarce [25, 26]. The few studies performed indicate that indeed some elderly patients themselves are not prepared to make the necessary changes to their lifestyle associated with dialysis [25]. The only study from Europe [26] provides some anecdotal evidence that although such patients enjoy life and express a desire to live for as long as possible, they are not prepared to do so at any price. In this small study, the age-associated decrease in vitality and loss of autonomy were important reasons for these patients to decline dialysis. Data from the dialysis outcomes and practice patterns study (DOPPS) [27] suggest that nephrologists take other factors into account. The medical directors of centers
participating in that study were asked about their agreement not to start haemodialysis in patients with specific conditions like dementia or multiple medical problems or in the very elderly and ‘not independent’ patients (nursing home residents). On average, they were hesitant not to start dialysis in these patients, but there was a huge variation across countries with UK nephrologists more often agreeing not to start dialysis than those from other countries. Nephrologists tended to agree more if patients were demented, but in the case of very elderly or dependent patients (nursing home residents), they usually disagreed with not starting dialysis. Recent data from the USA show that the dialysis outcomes in nursing home residents are not very good [1] and therefore suggest that it may not be possible to prolong life and increase the quality of life by dialysis in all patients with ESRD.

**Benefit or burden**

Nephrology is increasingly dominated by problems traditionally considered to be geriatric issues. As a result, there is an increasing debate whether dialysis in elderly patients should be considered a benefit or a burden and whether ‘non-aggressive renal care’ with prescription of relevant medication and diet should not deserve a more prominent place in ESRD [28]. Treatments to minimize the effects of uraemia and therefore postpone the need for dialysis may include erythropoetin, dietary restrictions, anti-hypertensive drugs, phosphate binders, calcium and vitamin D supplements. In theory, these interventions without dialysis would control blood pressure, nutritional status and uraemia and would avoid dialysis-related complications. Studies have shown that a strategy to postpone dialysis is probably a viable option in elderly patients with many comorbidities and a limited life expectancy [29–34]. From this perspective, the recently revised clinical practice guideline *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis* [35] is important. This guideline, however, is primarily based on the US data concerning options within US renal practice which may not reflect renal practice in Europe. The increasing prevalence of dialysis patients results in higher costs of dialysis. At the same time, there is an increasing awareness that rational treatment does not need to be the same as ‘rationing’. In this context, it is important to determine and characterize in a multinational European study the fraction of ESRD patients attending a nephrology clinic who are postponing or not starting dialysis and instead receive relevant medication and diet (as a result of their own preference or based on their physician’s advice) and to compare their outcomes with similar patients starting dialysis.

Dialysis or the prescription of relevant medication and diet to postpone or not to start dialysis may affect patient survival and quality of life in potentially important, different ways. Therefore, in analogy with clinical trials investigating treatments with a major impact on day-to-day life, it is crucial to consider both survival and quality of life in any comparison of outcomes between dialysis start with a high renal function versus a low renal function, a high number of uraemic signs and symptoms versus a low number of uraemic signs and symptoms and starting dialysis versus not starting dialysis. In the future, this will support patients and nephrologists in making better informed choices.

**Summary**

In conclusion, there are limited data on how renal function, and uraemic signs and symptoms can be used to determine when dialysis should be initiated in elderly patients in order to optimize the quantity and quality of life. Furthermore, it is unknown to which extent residual renal function, these uraemic signs and symptoms and patients preference contribute to medical decision making in the daily practice of starting dialysis and how they affect the subsequent patient outcomes. Finally, it is unknown which are valid methods to measure renal function in advanced CKD which may be used for the decision making on the start of dialysis. The international EQUAL study intends to address these issues.

**The EQUAL study**

EQUAL has received funding from the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) and co-funding from the Dutch Kidney Foundation and the Italian Society of Nephrology to conduct an international prospective multi-centre cohort study in CKD patients >65 years progressing towards ESRD. Patients at the nephrology clinic with an eGFR of 20 mL/min/1.73 m² or lower (first ever and those who are referred with a kidney function already below this level) will be recruited.

<table>
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<tr>
<th>Table 1. Synopsis of data collected within the EQUAL study</th>
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<td>History and physical examination</td>
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<td>• Lifestyle</td>
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<td>• Comorbidities</td>
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<td>• Uraemic signs and symptoms</td>
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<td>Lab and other investigations</td>
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<tr>
<td>• Blood: creatinine, urea, albumin, haemoglobin, haematocrit, mean corpuscular volume (MCV), electrolytes, parathyroid hormone (PTH) and cholesterol</td>
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<td>• 24-h urine: volume, creatinine, urea and protein</td>
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<td>• Tracer studies in a subset of patients to determine renal function</td>
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The research questions to be addressed include:

- How do uraemic signs and symptoms develop during the progression of CKD towards the start of dialysis?
- After accounting for biases such as lead-time bias and selection bias, how do the outcomes—in terms of patient survival and quality of life—compare between the start of dialysis with a higher renal function versus that with a lower renal function and the start of dialysis with fewer uraemic signs and symptoms versus that with more signs and symptoms?
- Which method of measuring renal function best informs the decision to start dialysis in advanced CKD?
- What is the best moment to start dialysis in terms of renal function and uraemic signs and symptoms in relation to subsequent outcomes?
- How does decision making of nephrologists and patients and their carers take place to decide if and when to start dialysis and by which factors is this affected?
- Are patients satisfied with decision making around the start or postponement of dialysis?

Baseline and follow-up data will include routine clinical data like demographics, lifestyle, comorbidities, uraemic signs and symptoms, data derived from physical examination (for example, nutritional status), routine blood and urine biochemistry, medication and other treatment characteristics as well as hospitalization and mortality (Table 1). In addition, data collection will comprise quality of life data, information on decision making including patients preferences and patients satisfaction. Individual participating countries may collect additional data for specific topics of interest and ancillary studies will be implemented. Tracer studies for measuring renal function using iohexol clearance in a subset of patients are included in this additional data collection both at patient inclusion and at the initiation of dialysis. At the same time points, blood and urine samples will be obtained from all patients for biobanking and central analysis in addition to standard clinical care.

Patients will be followed until death, discharge from the nephrology clinic to primary care or until the end of the study after 4 years of follow-up (Figure 1). Follow-up visits will take place every 6 months until the eGFR falls <10 mL/min/1.73 m² or the patient commences dialysis when the frequency will be increased to 3-month intervals. After 6 months on dialysis, the frequency of visits will return to every 6 months.

Specific statistical techniques like marginal structural modelling and inverse probability weighting will be employed to overcome selection bias which is inherent in observational studies. Such approaches have been successfully adopted in other areas of medicine to overcome confounding by indication and selection bias [36, 37]. We strive to include 3500 patients from five countries (Germany, Italy, Sweden, The Netherlands and the UK). A pilot study has been started in January 2012.

Conflict of interest statement. None declared.

References


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*Received for publication: 31.12.11; Accepted in revised form: 19.5.12* 

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**The EQUAL study**

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