Influence of early dialysis among patients with advanced chronic renal disease: results of a systematic review

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Introduction

Chronic renal disease is a progressive disorder with multiple causes, leading to irreversible loss of endogenous kidney function, so that patients come to depend upon renal replacement therapy (RRT). In Spain, as in the USA and Europe, diabetes mellitus is the most frequent cause of end-stage renal disease [1–3], accounting for almost a quarter of all incident patients in 2007 (22.4%) and displaying a rising trend. In 2007, >4500 patients started renal therapy in Spain, amounting to an incidence of 125 patients per million population [1], with increasingly older patients being admitted to treatment [4], a phenomenon that generates a considerable use of health resources and an ensuingly significant increase in costs [5].

International registries indicate that there have been no significant improvements in the survival of such patients, with wide age-related variations in evidence. Whereas subjects under the age of 44 years register an 84.5% survival rate at 5 years, this same rate is <20% among the >75-age group [3]. Insofar as treatment modality is concerned, transplanted patients register a 5-year survival of 86.5% versus 50% for dialysis patients, with cardiac causes being the principal cause of death in Europe. Since 2001, there has been an increase in mortality in Spain of close on 1.2% for haemodialysis (HD) compared to a decrease of >2% for peritoneal dialysis (PD), with an overall mortality of 8% in 2007 [1].

At present, there is no uniform criterion as regards the optimal time for initiating RRT. In theory, early initiation would improve nutritional status and cardiovascular complications, which would in turn mean a decrease in the earliest stages of dialysis in both mortality and the costs associated with these complications, although it would also expose patients to the complications of dialysis before this was strictly necessary, thereby raising the risk of infections and having a considerable impact on the quality of life of patients and their families [6,7]. Nevertheless, it is very complicated to study the effect of early initiation since it is very difficult to separate its effect from the lead-time bias that is present in many studies.

This study sought to use a systematic review of the scientific literature to analyse the influence of time of initiation of dialysis on the morbidity, mortality and quality of life of patients with chronic renal disease according to the glomerular filtration rate (GFR), in cases where initiation is based on residual kidney function at the date of commencing RRT.

Materials and methods

Search of the literature

In July 2008, a systematic review was made of the scientific literature. The following databases were consulted: MEDLINE; EMBASE; Cochrane Collaboration; National Health Service (NHS) Centre for Reviews and Dissemination, which includes Health Technology Assessment (HTA), Database of Abstracts of Reviews of Effectiveness (DARE) and NHS Economic Evaluation Database (NHS EED); and the Institute for Scientific Information (ISI) Web of Knowledge. This search was subsequently updated in October 2008 and in February 2009. To locate clinical research studies, we also searched the databases of ClinicalTrials.gov, National Research Register and other international registries, such as Current Controlled Trials or Center Watch. To collect other information of interest, manual searches targeted national databases and databases of recognized organizations and scientific societies. Specific search strategies were drawn up for each database, using different combinations and variations of search terms, such as ‘renal insufficiency’, ‘renal replacement therapy’ or ‘renal dialysis’. A manual search was likewise made of the references cited in all papers included.

Inclusion and exclusion criteria

The only studies included were those that met pre-established selection criteria defined in line with the objectives of this review. This meant that, in terms of: (i) study design, selection was limited to systematic reviews,
meta-analyses, clinical trials and cohort studies; (ii) sample size, a minimum of 20 patients was required, and in the case of studies with a parallel comparison group, only those with a minimum of 10 patients in each arm were eligible; (iii) patient characteristics, subjects were required to be adult patients with advanced chronic renal disease (stage III; GFR ≤ 60 mL/min/1.73 m², NKF criterion); (iv) follow-up, studies had to have a minimum of a 2-month follow-up from initiation of dialysis; (v) outcome variables, studies had to assess mortality, morbidity or quality of life to be eligible; (vi) exposure variables, patients had to be undergoing any dialysis or renal replacement therapy modality, with the exception of haemofiltration or modalities in a development stage; (vii) language, studies were limited to those published in English, French, Italian, Portuguese or Spanish. All search results were separately reviewed by two researchers, who then decided on a consensus basis which papers were to be retrieved for critical perusal of the complete text and rigorous data extraction.

Thereafter, the two reviewers separately conducted blind assessments of the study quality, applying a specifically adapted scale that had been previously used for haemodialysis studies [8–10]. In addition, the US Preventive Services Task Force grading scale was also used to rate the quality of scientific evidence [11].

Results

Search results

The bibliographic search yielded a total of 1463 references. As can be observed in Figure 1, only 10 met the pre-established inclusion criteria. These were all cohort studies, mostly published from 2002 to 2007. The origin of the papers varied, with three coming from the USA [12–14], another three from Europe [15,16], two from Asia [17,18], one from Australia [19], and one from Canada and the UK as the result of collaboration between research groups working in these two countries [7]. Individual study sample sizes ranged from 117 to 302 287 patients, with both haemodialysis and peritoneal dialysis being used as treatment modalities. Evidence tables listing the characteristics of all the studies included are shown in Table 1.

Early versus late initiation

Of the studies retrieved, nine analysed the influence of early or late initiation of dialysis on patient morbidity and mortality, and the 10th assessed its impact on quality of life [20]. Seven of the retrieved studies classified patients into two groups using different kidney function values, namely 5 [14,17], 7–8 [13,15,16] and 10 mL/min [18,19]. The two remaining studies [7,12] compared different ranges, namely <5, 5–10 and >10 mL/min. The studies that initiated treatment with high kidney function values, i.e. >7.5 mL/min, as well as the studies that compared different ranges of kidney function (<5, 5–10, >10), coincided in supporting a delay on treatment initiation, since they registered increases of 10–40% in risk of death with early initiation, though these studies mostly included patients treated with HD [7,12,13,15]. Korevaar, Cooper and Tang, in contrast, supported the initiation of treatment with high kidney function values (7–10 mL/min) because they associated this with improvements in survival and nutritional status, though these authors mainly included patients treated with PD [16,18,19]. The studies initiating dialysis with values <5 mL/min reported contradictory results. Whereas Shiao et al. [14] associated early initiation of treatment with improvement in nutritional status, Arora

![Fig. 1. Diagram of selection of papers.](image-url)
<table>
<thead>
<tr>
<th>Author, year and place</th>
<th>Type of study</th>
<th>Sample size</th>
<th>Population characteristics</th>
<th>Results</th>
<th>Conclusions of authors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>USPS Task Force</strong></td>
<td><strong>Scale Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiao et al. 2007 Asia</td>
<td>Retrospective cohort N=275</td>
<td>(51 years) (M: 51%) Nephrological reference (≥6 or &lt;6 months) Catheter implantation: Planned: N=58 (refer &gt;6: 81%) Late: N=217 (refer &gt;6: 33%)</td>
<td>Late initiation of dialysis: better survival (p=0.012) less risk of all-cause hospitalisation (p=0.025)</td>
<td>Do not support early initiation of PD. Stress importance of planning in catheter implantation.</td>
<td>II-2 5.9</td>
</tr>
<tr>
<td>Tang et al. 2007 Asia</td>
<td>Prospective cohort 1 year N=233</td>
<td>N Age (years) Sex (%) GFR initiation (ml/min)</td>
<td>Mortality at one year: 6.6% early versus 18.3% late (p=0.004) Survival 3.01 in favour of early treatment (95%CI, 1.32-9.40)</td>
<td>Initiation of treatment at onset of uroaemic symptomatology regarded as too late.</td>
<td>II-2 7.2</td>
</tr>
<tr>
<td>Wilson et al. 2007 Canada</td>
<td>Retrospective cohort 2 years N=271</td>
<td>N Age (years) Sex (%) GFR initiation (ml/min)</td>
<td>Mortality at 2 years: 17.1% late versus 41.7% early (p=0.022) (after adjustment for demographic variables, comorbidity, associated treatments and GFR at initiation, benefit of late initiation disappears) Use of antihypertensives independently affects on mortality at 2 years.</td>
<td>Initial health status suggested to be a decisive factor of survival at 2 years, and more important than time of initiation of dialysis.</td>
<td>II-2 5.9</td>
</tr>
<tr>
<td>Kazmi et al. 2005 USA</td>
<td>Retrospective cohort N=302,287</td>
<td>N Age (years) Sex (%) GFR initiation (ml/min)</td>
<td>Patients who initiated dialysis with GFR&gt;10 registered a 42% risk of death than those who initiated with GFR&lt;5.</td>
<td>Higher GFR at initiation related to higher risk of death. Initiating dialysis prior to GFR&lt;10 is not apparently a good prognostic marker.</td>
<td>II-2 3.9</td>
</tr>
<tr>
<td>Beddhu et al. 2003 USA</td>
<td>Prospective cohort N=2,920</td>
<td>N Age (years) Sex (%) Race (%) GFR (ml/min) Dialysis (%)</td>
<td>GFR (MDRD): every 5 ml/min causes 14% risk of death. (HR: 1.14; 95%CI, 1.06-1.22) Using formula C-G (Clcr) HR:1.08</td>
<td>Not enough evidence to support early initiation of dialysis. Deemed that patients with obvious clinical indications</td>
<td>II-2 7.4</td>
</tr>
<tr>
<td>Author, year and place</td>
<td>Type of study</td>
<td>Sample size</td>
<td>Population characteristics</td>
<td>Results</td>
<td>Conclusions of authors</td>
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</tr>
<tr>
<td>Cooper et al. 2003</td>
<td>Retrospective cohort</td>
<td>8.5 years</td>
<td>N=134</td>
<td></td>
<td>Direct relationship between kidney function and total nitrogen ($r^2=0.21$, p&lt;0.0001). 40% patients with Clcr&lt;10 at initiation are more malnourished.</td>
</tr>
<tr>
<td>Traynor et al. 2002</td>
<td>Retrospective cohort</td>
<td>N=235</td>
<td></td>
<td>Significant inverse relationship between Clcr and survival RR=1.1 (95%CI, 1.01-1.21, p=0.024). Slight and significantly ↑ risk of death with early initiation of dialysis</td>
<td>No support for early initiation of dialysis.</td>
</tr>
<tr>
<td>Korevaar et al. 2001</td>
<td>Multicentre prospective cohort</td>
<td>2 years</td>
<td>N=255</td>
<td>* ↑ risk of death with delay in dialysis. (↑ 22% risk of death with delay in initiation that may indicate ↓ GFR 1 ml/min/1.73m$^2$) Survival at 3 years: 2.5 months in favour of early initiation.</td>
<td>Benefit of incorporating DOQI recommendations into clinical practice is questioned, despite apparent benefit of early initiation.</td>
</tr>
<tr>
<td>Arora et al. 1999</td>
<td>Retrospective cohort</td>
<td>N=135</td>
<td></td>
<td>Initiation GFR&lt;5 more frequent between LR and hypoaalbuminaemia; less frequent ↑ age and white race.</td>
<td>Late referral to nephrologist is cause of delay in initiation of dialysis.</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; PD, peritoneal dialysis; HD, haemodialysis; Clcr, creatinine clearance; M, men.
et al. [17] supported a delay since they considered it to be associated with better survival and lower risk of hospitalization, though they mostly included patients treated with peritoneal dialysis. When analysis was performed by subgroups, all studies that delayed treatment initiation reported the presence in the early-initiation group of older patients and a greater proportion of men and diabetics, differences that rose as high as 25% and 30%, respectively. Insofar as treatment modality was concerned, studies that solely assessed patients treated with haemodialysis [7,12] indicated a higher mortality in the early-initiation group (GFR >10, age = 65–71 years). In contrast, studies that solely assessed peritoneal dialysis [17,18] yielded contradictory results, displaying a heterogeneous distribution by sex and co-morbidity (GFR ≥5–10, age = 56–57 years). The results of the studies included, broken down by GFR function at dialysis initiation can be observed in Table 2.

### Quality-of-life results

The influence of the time of initiation of dialysis on quality of life was only assessed by Korevaar et al. [20], as a second part of a previous study [16]. For the purpose, they used the Kidney Disease and Quality of Life Short Form questionnaire (KDQOL-SF36) in the first year of treatment. During the first months of treatment, a substantial improvement was observed in all groups, and the categories were evaluated (physical functioning, general health, bodily pain, vitality, etc.). The late-initiation group reported a worse perceived quality of life in most of the dimensions analysed, and in physical functioning.

### Table 2. Study results according to value of kidney function at initiation of treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>GFR mL/min</th>
<th>Early (ER)</th>
<th>Late (LR)</th>
<th>Results (ER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arora [14]</td>
<td>GFR ≥5 5</td>
<td>GFR &lt;5 n = 30 p, 7% PD</td>
<td>Age = 55 years (M: 44%) 40% DM</td>
<td>Improvement in nutritional status</td>
</tr>
<tr>
<td>Shiao [17]</td>
<td>GFR ≥5 110</td>
<td>GFR &lt;5 n = 165 p, 100% PD</td>
<td>Age = 48 years (M: 32%) 12% DM</td>
<td>† Mortality</td>
</tr>
<tr>
<td>Beddhu [13]</td>
<td>GFR &gt;7.5 7–10</td>
<td>GFR &gt;5 n = 1476 p, 52% HD</td>
<td>Age = 57 years (M: 49%) 34% DM</td>
<td>† Mortality (↑14% risk per ↑ 5 mL/min in kidney function)</td>
</tr>
<tr>
<td>Traynor [15]</td>
<td>GFR &gt;7.1 7–10</td>
<td>GFR &gt;5 n = 1444 p, 53% HD</td>
<td>Age = 61 years (M: 57%) 30% DM</td>
<td>† Mortality (↑10% risk per ↑ 1 mL/min in kidney function)</td>
</tr>
<tr>
<td>Korevaar [16]</td>
<td>GFR &gt;7.1 7–10</td>
<td>GFR &gt;5 n = 119 p, 69.7% HD</td>
<td>Age = 61 years (M: 77.3%) 32.7% DM</td>
<td>† Risk of death</td>
</tr>
<tr>
<td>Cooper [19]</td>
<td>GFR &gt;10 7–10</td>
<td>GFR ≤10 n = 108 p</td>
<td>Age = 61 years (M: 38%) 16.6% DM</td>
<td>Improvement in nutritional status</td>
</tr>
<tr>
<td>Tang [18]</td>
<td>GFR ≤10 7–10</td>
<td>GFR ≤10 n = 116 p, 75% HD</td>
<td>Age = 56 years (M: 56%) 10.3% DM</td>
<td>† Mortality</td>
</tr>
<tr>
<td>Kazmi [12]</td>
<td>GFR &gt;10 7–10</td>
<td>GFR ≤10 n = 82 p, 100% PD</td>
<td>Age = 56 years (M: 53.7%) 47.6% DM</td>
<td>† Mortality</td>
</tr>
<tr>
<td>Wilson [7]</td>
<td>GFR &gt;10 7–10</td>
<td>GFR ≤10 n = 82 p, 100% PD</td>
<td>Age = 56 years (M: 53.7%) 47.6% DM</td>
<td>† Mortality</td>
</tr>
<tr>
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<td>GFR &gt;10 7–10</td>
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<td>† Mortality</td>
</tr>
</tbody>
</table>

p, patient; PD, peritoneal dialysis; HD, haemodialysis; DM, diabetics; GFR, glomerular filtration rate.
and bodily pain in particular, though these differences disappeared at the end of 1 year, since this group registered more pronounced increases in all functions, obtaining similar scores.

Results of ongoing clinical trials

The bibliographic search retrieved an ongoing clinical trial, being undertaken in Australia and New Zealand on a total of 828 participants [21]. This is the Initiating Dialysis Early and Late (IDEAL) Study, directed to ascertain the influence of time of initiation of dialysis on the survival of patients with renal disease, and its impact on nutritional and cardiac status, quality of life, and costs. This study began in July 2000 and is expected to continue until the end of 2009, thus rendering it necessary to wait until the results are published, according to schedule, at least in 2010.

Study quality results

After using the scale adapted for this review, the scores awarded separately and blindly by two researchers coincided. The median and mean scores were 5.9 and 5.5 points, respectively. The study, which obtained the lowest score, was that by Arora [14], with 2.2 points, and the study, which obtained the highest score, was that by Beddhu [13], with 7.4 points. The scores obtained by each of the studies are shown in Figure 2.

Discussion

On the basis of currently available evidence, no conclusions can be drawn as to the optimal time for initiating renal replacement therapy, inasmuch as the results of the studies retrieved are contradictory, and moreover, there are methodological shortcomings that qualify the validity of their results. The main limitation is the presence of lead-time bias in the great majority of the included studies, which limits the interpretation of the results.

Lead-time bias in dialysis initiation has been defined as a prolonged survival for those patients initiating dialysis earlier which is not related to the physiological effect of dialysis but related to patient’s greater residual renal function. If this bias is present, an erroneous survival benefit is attributed to the early referral of patients to dialysis, when this increase is only due to the fact that patients survive more time on dialysis. Early referral results in earlier initiation of dialysis and prolongs survival on dialysis but does not change patient survival. The issue of how to correct for lead-time bias and when is the best time to start dialysis is a matter of controversy [18]. In the present review, most of the studies present lead-time bias. This bias cannot be corrected if the study is retrospective, but its effect can be taken into account in prospective designs. For example, the study by Tang et al. [18] tracked outcomes of all subjects from the point-in-time dialysis was recommended to them. This methodology eliminates the possible influence of lead-time bias. Regrettably, most of the studies are retrospective and therefore can present lead-time bias. It would be very interesting to know how much time elapses from a GFR of 12–10 mL/min to a GFR 7–5 mL/min. This time could provide an estimation of the lead-time bias and therefore could be deducted from the survival results of those arms assessing early initiation. An estimation of this time is given in the study by Tang et al. [18]. A mean time of 3.3 months elapsed since individuals were offered dialysis until the development of symptomatic uraemia and therefore initiation of dialysis. The question as to whether this time is clinically relevant or not is debatable, and falls outside the scope of this paper. In any case, lead-time bias has to be considered when interpreting these results.

Most clinical practice guidelines recommend dialysis initiation when kidney function falls below 15 or 10 mL/min and uraemia or malnutrition are present, and, as a rule, immediately in any case where kidney function falls below 6 mL/min [22–26]. Nevertheless, nephrologists’ decisions are based not only on kidney function value but also on a combination of clinical symptoms, laboratory parameters and individual factors [20,27–29], though at present, no clear consensus exists. Some studies indicate that early dialysis initiation proves prejudicial for the patient because it has been associated with an increased risk of death [7,12,13,15,17], yet the distribution by sex and co-morbidity has not been homogeneous in all cases, with the early-initiation group displaying a higher proportion of men and diabetics, a factor that underestimates survival in this group.

In theory, early initiation of dialysis would improve patients’ nutritional status and decrease cardiovascular com-
plications, mortality in the early stages of dialysis, and costs associated with such complications [6,7]. Aside from affording other advantages, such as improving patient rehabilitation or preventing the need for emergency dialysis [29]. In emergency situations, percutaneous vascular accesses (venous catheters) are used, which are associated with a higher risk of developing infections, thrombosis or stenosis [30], and some authors have observed that initial access via catheter entails a 2-fold risk of death (95% CI 1.35–3.51, P = 0.001) [15]. Nonetheless, it does prematurely expose the patient to dialysis-related complications, such as risk of peritonitis in peritoneal dialysis or more rapid loss of kidney function in the case of haemodialysis. Early initiation of treatment could have an important impact on organization, requiring an increase in staff and, most probably, in dialysis units, thereby inevitably generating an increase in costs, since it would raise the number of prevalent patients in haemodialysis [27]. Furthermore, it would oblige patients to observe a series of dietary restrictions and significantly impact on their quality of life [6,7]. It should be stressed that psychological factors, such as depression, anxiety, behavioural changes, lack of motivation and family support, influence the progress of such patients, and of young patients in particular [31].

Diverse strategies, which support early treatment initiation, are based on the hypothesis that early initiation improves nutritional status and reduces mortality [13] because, as the glomerular filtration rate decreases, so do protein intake and serum albumin values [32], that is to say, patients’ nutritional status at initiation of treatment is probably maintained despite intensive interventions [19]. Moreover, the results suggest that the poorer the initial nutritional status, the greater the decline in survival [14,19,33].

In terms of treatment modality, peritoneal dialysis displays certain advantages over haemodialysis, in that the initial stages of the former ensure that residual kidney function is better maintained, interfere less in patients’ quality of life and enable the entire vasculature of the upper limbs to be reserved for subsequent uses [34,35]. During the first 3 months of treatment, haemodialysis leads to a more pronounced decrease in kidney function, which considerably restricts patients’ lifestyles, influencing their morbidity and mortality [6,36].

The studies included in this review, which solely assessed patients undergoing haemodialysis, [7,12] reported a higher mortality among patients who initiated treatment early. In contrast, while studies that solely assessed peritoneal dialysis [17,18] indicated better survival with early initiation in one case [18] and reported contradictory results in the other, though here, distribution by sex and co-morbidity was not homogeneous [17]. With respect to studies which analysed comparable proportions of both dialysis modalities, in one case [13], these indicated a 1.4-fold rise in the risk of death for every increase of 5 mL/min in kidney function at initiation of treatment, and in the other a small beneficial effect in favour of early initiation [16]. Although this effect was not statistically significant, it could nevertheless be clinically relevant, since this group of patients displayed a slight advantage in their quality of life during the first months of treatment [37].

In our review, only one study analysed quality of life, using the KDQOL-SF36 questionnaire [37]. During the first 6 months of treatment, there was a notable improvement in the quality of life of all patients, regardless of the treatment modality used (haemodialysis or peritoneal dialysis). In contrast, patients who initiated treatment early showed greater improvement in some dimensions of the KDQOL immediately after initiating the treatment, though these differences disappeared after the space of 1 year. This improvement, albeit brief, could justify early initiation of treatment, should the results reported in various studies prove consistent. Similar results were obtained in a multicentre study undertaken in Europe, where patients who were referred early to the nephrologist, especially those who planned their first dialysis, registered better quality-of-life scores [38]. In practice, however, one of the reasons for which patients delay initiation of therapy is to enjoy more time without the restrictions associated with the treatment, particularly among patients who display better uraemia toleration.

The low quality of the studies retrieved means that the validity of the results obtained is diminished. In no case was randomization used for allocation of patients to the different groups, and the studies relied on short follow-up periods, and showed a high degree of heterogeneity in terms of patients’ age and distribution by sex and co-morbidity. All this hinders comparison of results and diminishes their validity. It is highly likely that, rather than reflecting the effect of time of initiation of dialysis, the results obtained in this review reflect the effect of the composition of the subgroups compared. Insofar as modality of initiation is concerned, the results obtained appear to indicate that early initiation of RRT yields worse results in haemodialysis than it does in peritoneal dialysis, registering an increase in risk of death of 10–14%. Many authors consider that initial health status or pre-dialysis care received are more relevant factors than time of initiation per se, highlighting the importance of a programmed initiation of dialysis, from both a clinical and a financial standpoint. With respect to quality of life, this cannot be claimed to be better among patients who initiate treatment early, since it was only assessed by one of the studies included. Well-designed, randomized studies of good methodological quality and taking into account lead-time bias are called for to ascertain in which population subgroups early initiation of RRT would be more beneficial and to assess its impact on patients’ quality of life.

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