Original Articles

Level of renal function in patients starting dialysis:
an ERA-EDTA Registry study

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Abstract

Background. The aims of this European study were (i) to compare the level of renal function at the start of dialysis between age groups, gender, primary renal disease, comorbid conditions, treatment modality, time periods and countries, and (ii) to determine which baseline characteristics are associated with the level of renal function at the start of dialysis.

Methods. Renal registries participating in the European Renal Association–European Dialysis and Transplant Association Registry provided data on serum creatinine 0–4 weeks before the start of dialysis in incident dialysis patients in 1999 and 2003. Data were available in 11 472 patients from nine renal registries. Glomerular filtration rate (GFR) was estimated by the four-variable Modification of Diet in Renal Disease equation.

Results. The unadjusted median eGFR at the start of dialysis was 7.0 mL/min/1.73 m2 in the 1999 data (median serum creatinine 7.5 mg/dL) and 7.7 mL/min/1.73 m2 in the 2003 data (serum creatinine 7.0 mg/dL). Using linear regression with adjustment for the other covariates, older patients, males, patients with diabetes mellitus, hypertension/renal vascular disease (HT/RVD) as primary renal disease (vs glomerulonephritis), ischaemic heart disease or peripheral vascular disease and patients starting on peritoneal dialysis (PD) initiated dialysis at higher levels of eGFR (range Δ eGFR: 0.1–1.2 mL/min/1.73 m2). Using the same analyses, eGFR differed between countries (range: 6.5–8.6 mL/min/1.73 m2).

Conclusions. During 2003, patients started dialysis at somewhat higher eGFR levels than those starting during 1999. There were also international differences in eGFR. Such differences may, at least in part, be explained by differences in creatinine measurement methods between countries and time periods. Finally, older patients, males, patients with HT/RVD or comorbidity and those starting on PD had slightly higher eGFR levels than younger patients, females, those with glomerulonephritis, without comorbidity and those starting on haemodialysis. Further research is needed into other, more clinically related factors affecting the decision to start dialysis.

Keywords: dialysis start; end-stage renal disease; epidemiology; glomerular filtration rate; serum creatinine

Introduction

Since 1997, clinical practice guidelines have included recommendations on the timing of initiation of dialysis [1–4]. The first guidelines of the National Kidney Foundation–Dialysis Outcome Quality Initiative (NKF–KDOQI) on this topic outlined that dialysis should be initiated when the weekly renal Kt/Vurea falls <2.0 [corresponding to a glomerular filtration rate (GFR) of about 10.5 mL/min], unless all three of the following criteria are fulfilled: stable or increased oedema-free body weight, no evidence of malnutrition (normalized protein equivalent of total nitrogen appearance ≥0.8 g/kg/day), and absence of clinical symptoms and signs attributable to uraemia. The 2006 update of these guidelines mentioned that when patients reach an estimated GFR <15 mL/min/1.73 m2, nephrologists should evaluate the benefits, risks and disadvantages of beginning kidney replacement therapy. The first European guidelines published in 2002 recommend that dialysis should be instituted whenever the
GFR is <15 mL/min/1.73 m² and there are clinical indications (i.e. symptoms or signs of uraemia, inability to control hydration status or blood pressure, or a progressive deterioration in nutritional status). Additionally, to ensure that dialysis started before the GFR is <6 mL/min/1.73 m², clinicians should aim to start at 8−10 mL/min/1.73 m². The 2005 update of the European guideline provided similar recommendations. These recommendations were largely based on extrapolation from observational and interventional studies showing a relationship between dialysis ‘dose’ and survival, leading to a consensus amongst guideline developers that ‘early start’ was beneficial rather than delaying renal replacement therapy (RRT) until a point well below the level of clearance and associated with the best survival on dialysis [5–7].

Table 1. Baseline characteristics of incident dialysis patients in 1999 and 2003, by national or regional registry

<table>
<thead>
<tr>
<th></th>
<th>All countries</th>
<th>Belgium speaking</th>
<th>Belgium French speaking</th>
<th>Finland</th>
<th>Greece</th>
<th>Italy (Basilicata/Piedmont)</th>
<th>Spain (Valencian region)</th>
<th>UK (England/Wales)</th>
<th>UK Scotland</th>
</tr>
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<tbody>
<tr>
<td><strong>1999</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population (number)</td>
<td>4756</td>
<td>837</td>
<td>529</td>
<td>442</td>
<td>728</td>
<td>140</td>
<td>188</td>
<td>1466</td>
<td>426</td>
</tr>
<tr>
<td>RRT</td>
<td>7046</td>
<td>880</td>
<td>679</td>
<td>452</td>
<td>1282</td>
<td>505</td>
<td>594</td>
<td>2101</td>
<td>553</td>
</tr>
<tr>
<td>Dialysis</td>
<td>6951</td>
<td>867</td>
<td>655</td>
<td>451</td>
<td>1279</td>
<td>504</td>
<td>594</td>
<td>2081</td>
<td>550</td>
</tr>
<tr>
<td>Coverage of total dialysis population by the study (%)</td>
<td>68.4</td>
<td>96.5</td>
<td>80.8</td>
<td>98.0</td>
<td>56.9</td>
<td>27.8</td>
<td>31.6</td>
<td>71.5</td>
<td>77.5</td>
</tr>
<tr>
<td>Age at start of dialysis (years) median [25th–75th percentile]</td>
<td>66.1</td>
<td>68.7</td>
<td>69.3</td>
<td>62.0</td>
<td>66.0</td>
<td>70.9</td>
<td>66.0</td>
<td>63.1</td>
<td>66.2</td>
</tr>
<tr>
<td>Gender (male) (%)</td>
<td>60.0</td>
<td>54.6</td>
<td>60.3</td>
<td>62.0</td>
<td>60.3</td>
<td>61.4</td>
<td>59.0</td>
<td>62.3</td>
<td>58.7</td>
</tr>
<tr>
<td>Primary renal disease (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22.1</td>
<td>25.7</td>
<td>23.6</td>
<td>33.5</td>
<td>22.4</td>
<td>16.4</td>
<td>11.2</td>
<td>18.2</td>
<td>20.0</td>
</tr>
<tr>
<td>RVD/hypertension</td>
<td>15.9</td>
<td>23.2</td>
<td>19.5</td>
<td>8.4</td>
<td>10.3</td>
<td>32.9</td>
<td>18.6</td>
<td>14.0</td>
<td>13.9</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>13.0</td>
<td>10.6</td>
<td>11.3</td>
<td>13.1</td>
<td>16.8</td>
<td>11.4</td>
<td>15.4</td>
<td>12.5</td>
<td>14.6</td>
</tr>
<tr>
<td>Other</td>
<td>49.0</td>
<td>40.5</td>
<td>45.6</td>
<td>45.0</td>
<td>51.6</td>
<td>39.3</td>
<td>54.8</td>
<td>55.3</td>
<td>51.6</td>
</tr>
<tr>
<td>Haemodialysis at start (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (%)a</td>
<td>93.6</td>
<td>NA</td>
<td>NA</td>
<td>99.9</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>89.5</td>
<td>NA</td>
</tr>
</tbody>
</table>

|                         | 6716          | 1009              | 401                     | 474     | 1290   | 140                        | 229                      | 2617                | 556         |
| Total population (number) | 9880          | 1047              | 697                     | 482     | 1938   | 512                        | 676                      | 3926                | 602         |
| RRT                     | 9920          | 1045              | 695                     | 480     | 1933   | 507                        | 675                      | 3837                | 596         |
| Dialysis                | 67.8          | 96.6              | 57.7                    | 98.8    | 66.7   | 27.6                       | 33.9                     | 68.2                | 93.3        |
| Coverage of total dialysis population by the study (%) | 68.0          | 71.0              | 71.8                    | 64.9    | 69.1   | 68.9                       | 66.0                     | 66.1                | 67.1        |
| Age at start of dialysis (years) median [25th–75th percentile] | [55.2–75.7]   | [60.9–78.3]        | [59.1–78.3]             | [51.4–74.0] | [58.4–75.4] | [57.0–75.6] | [51.2–74.9] | [52.4–74.8] | [53.4–75.1] |
| Gender (male) (%)       | 60.9          | 56.0              | 62.6                    | 67.1    | 62.0   | 60.7                       | 59.8                     | 62.3                | 54.5        |
| Primary renal disease (%) |              |                  |                         |         |        |                            |                          |                     |             |
| Diabetes mellitus       | 23.1          | 24.1              | 24.7                    | 36.3    | 26.6   | 16.4                       | 14.9                     | 19.9                | 19.6        |
| RVD/hypertension        | 16.1          | 26.9              | 22.2                    | 5.9     | 13.0   | 24.3                       | 15.3                     | 14.1                | 15.3        |
| Glomerulonephritis      | 11.4          | 8.5               | 11.2                    | 12.7    | 13.7   | 10.0                       | 15.3                     | 10.7                | 12.1        |
| Other                   | 49.5          | 40.5              | 41.9                    | 45.2    | 46.7   | 49.3                       | 54.6                     | 55.3                | 53.1        |
| Haemodialysis at start (%) |             |                  |                         |         |        |                            |                          |                     |             |
| Caucasian (%)a          | 93.7          | NA                | NA                      | 99.8    | 100    | NA                         | NA                       | 88.9                | NA          |

Comorbidity at start of dialysis (%)b

<table>
<thead>
<tr>
<th></th>
<th>All countries</th>
<th>Belgium speaking</th>
<th>Belgium French speaking</th>
<th>Finland</th>
<th>Greece</th>
<th>Italy (Basilicata/Piedmont)</th>
<th>Spain (Valencian region)</th>
<th>UK (England/Wales)</th>
<th>UK Scotland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>8.4</td>
<td>NA</td>
<td>NA</td>
<td>2.1</td>
<td>10.4</td>
<td>NA</td>
<td>NA</td>
<td>8.6</td>
<td>NA</td>
</tr>
<tr>
<td>(comorbidity)c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30.5</td>
<td>NA</td>
<td>32.3</td>
<td>35.6</td>
<td>32.8</td>
<td>NA</td>
<td>NA</td>
<td>26.8</td>
<td>NA</td>
</tr>
<tr>
<td>(PRD or comorbidity)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>31.6</td>
<td>NA</td>
<td>29.2</td>
<td>28.5</td>
<td>40.3</td>
<td>NA</td>
<td>NA</td>
<td>24.8</td>
<td>NA</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>12.0</td>
<td>NA</td>
<td>13.7</td>
<td>8.3</td>
<td>14.0</td>
<td>NA</td>
<td>NA</td>
<td>10.8</td>
<td>NA</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>11.8</td>
<td>NA</td>
<td>17.0</td>
<td>13.3</td>
<td>9.3</td>
<td>NA</td>
<td>NA</td>
<td>12.2</td>
<td>NA</td>
</tr>
</tbody>
</table>

Percentages may not add up to 100% because of rounding off; eGFR, glomerular filtration rate (estimated with the abbreviated MDRD equation); RVD, renal vascular disease; NA, not available.

aData on race (i.e. percentage of Caucasian) for all countries were based on Greece, Italy and UK (England/Wales).

bDiabetes mellitus in addition to another renal disease.

cData based on 100% of the patients in Belgium (French speaking), Finland and Greece, and on 49% of the patients in the UK (England/Wales).
Results from a large American study, including more than 90,000 patients who began dialysis between 1995 and 1997, showed that the median GFR at the start of dialysis estimated by the Modification of Diet in Renal Disease (MDRD) equation was 6.6 mL/min/1.73 m² and that a quarter of the patients started dialysis by an eGFR of <5.1 mL/min/1.73 m² [8]. In addition, the level of renal function was shown to vary between different patient subgroups, for example by age groups and gender. Within Europe, data on (trends in) the level of renal function in patients starting dialysis were only available from a few small studies or annual reports [9–11].

The aims of this European study were (i) to compare the level of renal function at the start of dialysis between age groups, gender, primary renal disease, comorbid conditions, treatment modality, time periods and countries, and (ii) to determine which baseline characteristics are associated with the level of renal function at the start of dialysis.

Methods

Population and data collection
All national and regional renal registries participating in the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry with individual patient data at the time of the start of the study and with a follow-up until 31 December 2005 [12] were asked whether they could provide data on the last serum creatinine assessed in the 0–4 weeks before the start of dialysis in patients >20 years of age and starting dialysis in 1999 or 2003. These data were available in 11,472 patients in eight national or regional renal registries. In Belgium (Dutch and French speaking), Finland and UK (England/Wales), these data were already available in the renal registry database, whereas the renal registries in Italy (Basilicata, Piedmont), Greece, Spain (Valencian region) and UK (Scotland) collected these data retrospectively from the patients’ medical records in the renal centres. UK (Scotland) collected these data on all patients who started dialysis in 1999 and 2003, whereas the registries of Greece, Italy and Spain collected these data in a sample of the total incident dialysis population in these years. If available, the registries provided additional data on the date of the measurement of serum creatinine, race (Caucasian: yes/no) and comorbidity at the start of dialysis, including diabetes mellitus, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease and malignancy. We included comorbid conditions of which the definitions were comparable within the different European RRT populations [13].

Analyses
We calculated the percentage coverage of the total incident dialysis population and assessed if our study population in a country/region was a representative sample with regard to median age, and distribution of gender and renal disease of all incident dialysis patients in that country/region as known from the ERA-EDTA Registry database. We repeated the analyses for patients for whom a serum creatinine value was available but where the exact measurement date was missing. Additionally, we compared the median age, gender distribution and median eGFR for patients for which data on comorbidity were available with those of patients without these data.

In keeping with the guidelines on the initiation of dialysis [1,3], residual renal function was estimated by GFR (eGFR) with the four-variable MDRD equation [14,15]:

$$\text{GFR (mL/min/1.73 m²)} = 186.3 \times \left( \frac{\text{serum creatinine (mg/dL)}}{\text{age (years)}} \right)^{-1.154} \times \left( \frac{\text{race (Caucasian: yes/no)}}{1.209} \right)$$

For women, the calculated values are multiplied by 0.742.
For black people, the calculated values are multiplied by 1.212.

No attempt was made to allow for variation between different creatinine assays. Patients were included in the study if the date of the measurement of serum creatinine was 0–4 weeks before the start of dialysis as reported to the participating registry. If more than one serum creatinine assessment was available 0–4 weeks before the start of dialysis, the last measurement was used for the study. If information on race was unavailable, patients were categorized as Caucasian, as the vast majority of the European dialysis population is Caucasian [16]. Of the registries that provided data on race [Greece, Italy and UK (England, Wales)], >94% of the patients were Caucasian. Data on comorbidity were available for 3451 patients who started dialysis in 2003 (51.4%) in 100% of patients in Belgium (French speaking), Finland and Greece, and in 49% of the patients in the UK (England, Wales).

The distributions of eGFR and serum creatinine were right skewed. Median eGFR (mL/min/1.73 m²) and median serum creatinine (mg/dL) were calculated for incident dialysis patients in 1999 and 2003, for all countries together and for each country separately. Further analyses were performed by age group, gender, primary renal disease (PRD), treatment modality and comorbidity (the latter only for those countries where these data were available). A Mann–Whitney test was used to compare the continuous baseline characteristics, whereas the chi-square test was used to compare categorical baseline characteristics. However, as the vast majority of the differences were statistically significant as a result of the large sample size, P-values were not presented.

A linear regression analysis was used to examine which determinants were associated with the level of renal function at the start of dialysis. The association of each determinant with the level of eGFR at the start of dialysis was adjusted for the other covariates, i.e. age group, gender, primary renal disease, treatment modality, year of start and country. Adjustment for country was performed in order to adjust for differences in strategies regarding selection of patients for pre-emptive transplantation, creatinine measurement methods used and other differences in health care systems. The determinants on comorbidity were examined for those countries where data on comorbidity were available in the 2003 data. In these latter analyses, the association of the determinants with the outcome variable was adjusted for the other covariates, i.e. age group, gender, treatment modality and country. We transformed the dependent variable eGFR into log eGFR, as in this case the assumptions for the linear regression model were fulfilled. For an easier interpretation of the results, the beta coefficients of log eGFR were transformed back to eGFR (i.e. exp β – 1), representing the percentage change in eGFR compared to the reference group for categorical exposure variables [17]. Using the linear regression model, we could calculate the eGFR (mL/min/1.73 m²) for each determinant adjusted for fixed values of the other categorical covariates using their distribution (e.g. for gender: 60% male and 40% female). Analyses were performed using SAS 9.1.
Results

Baseline characteristics

Table 1 shows that the percentage of the dialysis population presented in the study (i.e., with data on serum creatinine) varied from 27.8% in the Italian sample to 98.0% in Finland. The patients for whom a creatinine value was available were representative of all patients starting dialysis in the same regions with respect to median age, and distribution of gender and PRD. Additionally, these baseline characteristics were similar in patients with a median age of [25th and 75th percentile]

GFR (ml/min/1.73 m²) | Serum creatinine (mg/dL)
--- | ---
7.0 [5.5-9.1] | 7.5 [5.9-9.4]
7.7 [6.0-10.3] | 7.0 [5.4-8.8]
7.4 [5.7-9.7] | 7.0 [5.5-8.9]
8.7 [6.4-11.6] | 6.0 [4.7-8.1]
7.9 [6.0-10.6] | 6.7 [5.0-8.6]
8.8 [6.4-12.0] | 6.0 [4.5-8.0]
6.2 [5.0-7.7] | 8.3 [7.0-10.0]
6.6 [5.3-8.3] | 7.9 [6.5-9.5]
7.0 [5.7-8.2] | 7.8 [6.3-9.0]
7.6 [6.3-9.4] | 7.0 [5.8-8.3]
7.4 [5.7-9.0] | 7.4 [5.9-8.7]
8.6 [6.7-10.7] | 6.4 [5.2-7.7]
6.8 [5.3-9.0] | 7.9 [6.2-10.0]
7.7 [6.0-10.1] | 7.1 [5.6-8.9]
6.7 [5.3-8.8] | 7.6 [6.1-9.7]
7.6 [5.9-10.3] | 6.9 [5.6-8.8]

Fig. 2. Median [25th and 75th percentile] eGFR (mL/min/1.73 m²) and serum creatinine (mg/dL) at the start of dialysis in 1999 and 2003, by country (unadjusted).
Fig. 3. Median [25th and 75th percentile] eGFR (mL/min/1.73 m²) and serum creatinine (mg/dL) at the start of dialysis in 1999 and 2003, by patient subgroup (unadjusted).
measurement date for serum creatinine compared to those for whom such a date was missing. Median age (67.6 vs 67.1 years), gender distribution (62.4 vs 59.7%) and median eGFR (7.4 vs 7.4 mL/min/1.73 m²) were similar for patients for which data on comorbidity were available (n = 3451) compared to those without data on comorbidity (n = 8021).

Table 1 shows the baseline characteristics of the incident dialysis patients in 1999 (n = 4756) and 2003 (n = 6716) in each of the participating registries. The median age at the
The start of dialysis was higher in patients who started dialysis in 2003 (68.0 years) compared to those who started dialysis in 1999 (66.1 years) (P < 0.001). This trend was found in each of the participating countries, with the exception of Italy and Spain (Valencian region). The prevalence of the four PRD categories did not differ between the 1999 and 2003 samples, whereas the percentage of patients on haemodialysis (HD) as first treatment was somewhat higher in 2003 (80.9%) than in 1999 (78.4%) (P < 0.001). Baseline characteristics differed between the participating registries, e.g. median age at the start of dialysis (2003 data: range 64.9–71.8 years), the prevalence of diabetes mellitus as PRD (range: 14.9–36.6%) and the percentage of HD as first treatment (range: 72.0–91.7%).

**Figure 1** shows the distribution of eGFR (mL/min/1.73 m²) in patients starting dialysis in 1999 and 2003. The absolute number of patients starting dialysis at an eGFR <6 mL/min/1.73 m² was almost similar in the 1999 and 2003 data, but the percentage decreased from 34.2% in 1999 to 25.5% in 2003. The increase in the number of patients starting dialysis in 2003 compared to 1999 fully consisted of patients starting at an eGFR ≥6 mL/min/1.73 m². The unadjusted median eGFR at the start of dialysis was 7.0 mL/min/1.73 m² in the 1999 data and 7.7 mL/min/1.73 m² in the 2003 data, and the unadjusted median serum creatinine at the start of dialysis was 7.5 mg/dL in the 1999 data and

### Table 2. Determinants of the level of eGFR (mL/min/1.73 m²) at the start of dialysis using linear regression analyses

<table>
<thead>
<tr>
<th></th>
<th>eGFR (mL/min/1.73 m²) adjusted for general characteristicsa (95% confidence interval)</th>
<th>Difference in eGFR (%) adjusted for general characteristicsa (95% confidence interval)</th>
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</thead>
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<td><strong>Age (years)</strong></td>
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<td></td>
</tr>
<tr>
<td>20–44</td>
<td>7.2</td>
<td>Ref</td>
</tr>
<tr>
<td>45–64</td>
<td>7.3 (7.1–7.4)</td>
<td>1.4 (−1.1; 3.9)</td>
</tr>
<tr>
<td>65–74</td>
<td>7.6 (7.4–7.8)</td>
<td>6.5 (3.9; 9.2)</td>
</tr>
<tr>
<td>75+</td>
<td>8.0 (7.8–8.2)</td>
<td>11.1 (8.2; 14.1)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
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<td></td>
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<tr>
<td>Women</td>
<td>7.0</td>
<td>Ref</td>
</tr>
<tr>
<td>Men</td>
<td>7.9 (7.8–8.0)</td>
<td>13.3 (11.5; 15.0)</td>
</tr>
<tr>
<td><strong>Primary renal disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8.4 (8.1–8.6)</td>
<td>16.9 (13.8; 20.1)</td>
</tr>
<tr>
<td>Hypertension/renal vascular disease</td>
<td>7.6 (7.3–7.8)</td>
<td>5.6 (2.6; 8.8)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>7.2</td>
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<tr>
<td>Other cause</td>
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<tr>
<td><strong>Treatment modality</strong></td>
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<td></td>
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<tr>
<td>Haemodialysis</td>
<td>7.5</td>
<td>Ref</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
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<td>4.8 (2.8; 6.9)</td>
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<tr>
<td><strong>Year of start</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>7.1</td>
<td>Ref</td>
</tr>
<tr>
<td>2003</td>
<td>7.9 (7.8–8.0)</td>
<td>11.2 (9.5; 12.9)</td>
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<td><strong>Countries</strong></td>
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<tr>
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<td>8.2</td>
<td>Ref</td>
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<tr>
<td>Belgium (French speaking)</td>
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<td>2.2 (−0.99; 5.6)</td>
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<td>5.9 (2.5; 9.4)</td>
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<td>Greece</td>
<td>6.5 (6.3–6.7)</td>
<td>−20.1 (−22.2; −18.0)</td>
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<td>−9.9 (−14.3; −5.1)</td>
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<td>Spain (Valencian region)</td>
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<td>2.3 (−2.1; 6.8)</td>
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<tr>
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<td>10.9 (7.6; 14.3)</td>
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<td>7.7 (7.5–8.0)</td>
<td>3.6 (0.30; 7.0)</td>
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<td>−1.7 (−5.8; 2.7)</td>
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<td>Ref</td>
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<td>7.8 (7.5–8.1)</td>
<td>4.2 (0.43; 8.2)</td>
</tr>
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<td>Ref</td>
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<tr>
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<td>7.3 (7.0–7.6)</td>
<td>−3.7 (−7.7; 0.48)</td>
</tr>
</tbody>
</table>

Ref, reference group.

aAdjusted for fixed values of age, gender, primary renal disease, treatment modality, year of start and country. The determinants of comorbidity were adjusted for fixed values of age, gender, treatment modality and country.

bData on comorbidity were available for the 2003 data of Belgium (French speaking), Finland, Greece and the UK (England/Wales).
7.0 mg/dL in the 2003 data. Comparing the 1999 data with the 2003 data, a higher unadjusted median eGFR and a lower unadjusted median serum creatinine were present in 2003 in each country (Figure 2) and in each patient subgroup (Figure 3), with an increase in median eGFR ranging from 0.4 to 1.4 mL/min/1.73 m². Figure 4 shows that in those countries in which comorbidity data were available (2003 data), the unadjusted median eGFR at the start of dialysis for patients with at least one comorbid condition ranged from 7.4 (malignancy) to 7.9 mL/min/1.73 m² (diabetes mellitus as comorbidity or PRD) and the unadjusted median serum creatinine from 7.1 (malignancy) to 6.9 mg/dL (diabetes mellitus and cerebrovascular disease).

Determinants of the level of renal function at the start of dialysis

Table 2 shows that, after adjustment for general characteristics using linear regression analyses, the eGFR (mL/min/1.73 m²) was 11.2% (95% confidence interval: 9.5: 12.9) higher in patients who started dialysis in 2003 (7.9 mL/min/1.73 m²) compared to those who started in 1999 (7.1 mL/min/1.73 m²). Furthermore, using the same analyses, older patients tended to start at higher levels of eGFR than younger patients (8.0 vs 7.2 mL/min/1.73 m²), males at higher levels of eGFR than females (7.9 vs 7.0 mL/min/1.73 m²), patients with end-stage renal disease (ESRD) due to diabetes mellitus or due to hypertension/renal vascular disease at higher levels of eGFR than those suffering from other primary renal diseases (diabetes mellitus: 8.4, hypertension/renal vascular disease: 7.6 vs glomerulonephritis: 7.2 mL/min/1.73 m²) and patients starting on peritoneal dialysis (PD) at higher levels of eGFR than those starting on HD (7.8 vs 7.5 mL/min/1.73 m²) (Table 2). The minimum and maximum difference in eGFR between these studied patient subgroups was 0.1 mL/min/1.73 m² (age group 20–44 vs 45–64 years and PRD glomerulonephritis vs other cause) and 1.2 mL/min/1.73 m² (diabetes mellitus vs glomerulonephritis), respectively. Table 2 also shows that eGFR at the start of dialysis differed between countries (range: 6.5–8.6 mL/min/1.73 m²). Results did not materially differ when the eGFR was adjusted for general characteristics and comorbidity in those countries for which comorbidity data were available.

In those countries in which comorbidity data were available (2003 data), patients with diabetes mellitus as comorbidity or PRD tended to start dialysis at higher levels of eGFR than those without diabetes mellitus, also after adjustment for general characteristics (8.1 vs 7.5 mL/min/1.73 m²) (Table 2). The difference in the level of renal function at the start of dialysis was only limited but still statistically significant in patients with ischaemic heart disease compared to those without ischaemic heart disease (7.7 vs 7.5 mL/min/1.73 m²) and in patients with peripheral vascular disease compared to those without peripheral vascular disease (7.8 vs 7.5 mL/min/1.73 m²). The level of renal function was similar for patients with and without the presence of cerebrovascular disease and malignancy. Determinants of the level of renal function at the start of dialysis did not differ when the level of serum creatinine was used or when data were analysed in the 1999 or 2003 data separately.

Discussion

This first large European study, including >11 000 incident dialysis patients, focusing on the level of renal function at the start of dialysis showed that the median eGFR was 7.0 mL/min/1.73 m² in the 1999 data and 7.7 mL/min/1.73 m² in the 2003 data. The data from this international study confirm the findings from the few other available studies that were based on national data only. For example, Obrador et al. showed that in a US study including 90 897 patients starting dialysis between 1995 and 1997, the mean and median GFR estimated by the six-variable MDRD equation were 7.1 and 6.6 mL/min/1.73 m², respectively [8]. Furthermore, the results of our study may suggest compliance to the guidelines as the level of renal function at the start of dialysis was higher in 2003 compared to 1999. Still, more than a quarter of the patients started dialysis below an eGFR of 6 mL/min/1.73 m², whereas the European guidelines recommend that dialysis is started before the GFR is <6 mL/min/1.73 m² [3,4]. This may be partially due to late referral, but it is unlikely that this substantial fraction can be explained by this factor alone.

In our study, the increasing trend in eGFR from 1999 to 2003 was found in each country and in each studied patient subgroup, including amongst patients with a better prognosis. The differences in eGFR between the studied patient subgroups were statistically significant but the absolute differences were small. Differences between countries were somewhat bigger. The potential explanations are discussed below.

Time trend in eGFR at the start of dialysis

The first question to answer is whether the increase in starting eGFR between 1999 and 2003 represents a ‘real’ increase in the amount of residual renal excretory function (GFR) at the time of start. A real time trend in eGFR may be caused by adherence to the guidelines or by a continuation of a potential time trend that started in an earlier period caused by other factors, for instance a relative increase in availability of dialysis facilities. On the other hand, an apparent increase (but unintended by the nephrologist) may be caused by changes in the formulae used for the calculation of eGFR in daily practice or by different methods in the measurement of serum creatinine.

Concerning the introduction of the guidelines on the timing of initiation of dialysis in 1997 (US KDOQI) [1] and 2002 (European Best Practice Guidelines—EBPG—and updated version of US KDOQI) [2,3], representatives from included registries confirmed that, whereas in 1999 very few countries used any guideline, in 2003 some followed the KDOQI, EBPG or the UK guideline. Therefore, the introduction of the guidelines may have had some effect on eGFR at the start of dialysis. However, a number of
other potential causes for this increase also need to be taken into consideration.

A recent paper by Hsu et al. showed that patients who started dialysis in the 1980s were more likely to receive dialysis at higher levels of renal function than patients who started in the 1960s, even after adjustment for several confounders [18]. Furthermore, the results of a Dutch study indicated a tendency towards a start of dialysis at higher levels of eGFR in the 1990s [10]. In this perspective, our results may just indicate a continuing tendency to start dialysis at higher levels of eGFR irrespective of any guidelines. Finally, a relatively increased availability of RRT facilities compared to the demand created by new ESRD patients may have contributed to a start of dialysis at higher levels of eGFR in 2003 compared to 1999.

However, other factors may also have contributed to a change in eGFR over time. First, different methods may have been used to estimate GFR in 1999 and in 2003. Although data on the formula used to assess eGFR were not available on the patient level, we know from personal communication with the participating registries that in 1999 the Cockcroft and Gault equation was most often used, whereas in 2003 the use of the MDRD formula was rising. Studies performed so far suggest that in low ranges of eGFR the Cockcroft and Gault equation may overestimate GFR, whereas the MDRD equation, although it seems to be less biased and more precise and accurate than the Cockcroft and Gault equation, may underestimate GFR [19–21]. We also know that the use of the MDRD equation will make eGFR values suffer from imprecision. Imprecision is known to result in higher P-values. Nevertheless, the differences found in this study were small but statistically significant. The influence of the increased use of the MDRD equation in the 2003 data on the estimation of GFR is not straightforward. A further source of bias may originate from different methods to measure serum creatinine. The most reliable method to assess serum creatinine is the enzymatic method, but this method is only rarely used within clinical practice. At our request, the representatives from included registries reported that the Jaffé method was the most often used method both in 1999 and in 2003, but there was no detailed information available about the different types of Jaffé tests. It is possible that the creatinine assays used in 1999 were different from the ones used in 2003, as over time creatinine assays have become less sensitive to non-creatinine chromogens, thus resulting in lower serum creatinine values and higher levels of eGFR. This change in methodology could at least in part explain the time trend in eGFR. It should be noted that, according to the representatives in the different countries, there were no changes in government or state policy on how laboratories should report estimated kidney function.

It is of interest to note that a recent study using US Renal Data System data showed that almost the entire increase in the incidence counts over the period 1996–2005 occurred in patients who started at higher levels of eGFR (eGFR >10 mL/min/1.73 m²) [22]. We confirm that a substantial part of the increased number of patients starting dialysis in 2003 consisted of patients starting ≥10 mL/min/1.73 m² (eGFR ≥10 mL/min/1.73 m²: increase of 100% from 909 to 1821 patients and eGFR <10 mL/min/1.73 m²: increase of 27% from 3847 to 4895 patients). Therefore, indeed, also in Europe at least a part of the increase in the incidence of RRT seems to be due to a start of dialysis at higher levels of renal function.

**Age and gender**

The MDRD formula tends to overestimate GFR in older people [20]. This may explain to some extent why older patients seem to start dialysis at higher levels of eGFR than younger patients, because if the physicians’ reliance is on clinical indications rather than estimates of GFR to decide on initiation, these clinical indications may occur at higher levels of eGFR (but the same true GFR) in older people compared to younger people. The difference in level of renal function according to age was more pronounced in the US data presented by Obrador et al. [8] compared with our study also after adjustment for potential confounders (~1.8 vs 0.8 mL/min/1.73 m²). This may suggest that US nephrologists tend to attach more importance to the factor of age when deciding on when to start dialysis.

In our opinion, there is no clear explanation why males have somewhat higher levels of eGFR at the start of dialysis compared to females as found in our study and in other studies [8,11]. It should be noted that the MDRD equation includes gender, aiming at taking into account that females have lower muscle mass resulting in lower serum creatinine.

**Primary renal disease and comorbidity**

Although the difference in eGFR at the start of dialysis between patients with and without diabetes mellitus was much more limited than we expected beforehand, our study results are in line with the recommendations of the guidelines and common belief that diabetic patients require a start of dialysis at higher levels of eGFR [1,3,4]. Nevertheless, the difference in our study was somewhat smaller than in the study by Obrador et al. [8] (difference in median eGFR was 0.6 vs 1.0 mL/min/1.73 m², respectively). Differences in the level of renal function at the start of dialysis between patients with and without the other assessed comorbid conditions were even less and also much smaller than we had expected. However, the difference in eGFR at the start of dialysis could be different for important comorbid conditions that could not be assessed in this study, like chronic heart failure.

**Treatment modality**

Our data confirm a somewhat lower eGFR (0.3 mL/min/1.73 m) in patients who started HD compared to those who started PD. A reason for this could be that patients who receive pre-dialysis care were more likely to start on PD, whereas those patients who were admitted for dialysis in an emergency setting will often start on HD [23].
International differences

Many of the potential explanations for the differences in starting eGFR within countries between 1999 and 2003 may also be a valid explanation for differences between countries, i.e. different methods to estimate GFR, different creatinine measurement methods, a different use of guidelines and the availability of RRT facilities might be relatively higher in some countries resulting in a start of dialysis at higher levels of eGFR. With regard to the latter reason, it is of interest to note that in a study from Jalisco (Mexico), where the availability of dialysis facilities is low, the mean eGFR at the start of dialysis in 2003 was much lower (3.9 mL/min/1.73 m²) compared to the current study [24]. It should be noted that the incidence per million population (p.m.p.) in Jalisco (Mexico) is higher (280 p.m.p.) than in European countries [25,26]. However, given the fact that country was the most important factor in the level of eGFR at the start of dialysis, we cannot exclude a real international difference in the strategy on when to start dialysis.

Confounding by indication

In this study, the timing of the initiation of dialysis was based on eGFR only. Unfortunately, other characteristics of the patient’s clinical condition that will very likely affect the nephrologist’s decision when to start dialysis could not be evaluated as risk factors for initiating dialysis at higher or lower levels of eGFR in addition to those investigated in this study. To our knowledge, there are no publications describing the effect of such clinical characteristics in a quantitative manner. Therefore, when making comparisons between the level of eGFR between age groups, gender, PRD, treatment modality, time periods, countries and comorbid conditions, the comparisons may suffer from confounding by indication in that there were other reasons than the ones investigated that contributed to a start at higher levels of eGFR. Exactly those other reasons will partly explain the remaining variation in eGFR at the start of dialysis. Despite adjustment for age, gender, PRD and comorbid conditions, without knowledge on the specific reason to start dialysis at a particular level of eGFR in a given patient, confounding by indication, especially in the comparisons between time periods and countries, cannot be fully ruled out.

Conclusion

The results of this large European study suggest that, based on the level of renal function alone, the guidelines’ eGFR thresholds were largely unmet in 1999 and 2003. Although 2003 patients started dialysis at somewhat higher eGFR levels than those starting in 1999, these results do not necessarily implicate increased compliance with the guidelines, as there was a concomitant change in creatinine measurement methods over time introducing a bias towards increased eGFR.

Although differences were only small, our data showed that older patients started at higher levels of eGFR than younger patients, males at higher levels than females, patients with ESRD due to diabetes mellitus or due to hypertension/renal vascular disease at higher levels than those suffering from glomerulonephritis, patients with DM, IHD or PVD at higher levels than patients without these conditions and patients starting on PD at higher levels of eGFR than those starting on HD. Given their limited size, these differences are potentially clinically irrelevant. Our study revealed that country was the most important factor for the level of eGFR at which dialysis was started, although it is possible that international differences in creatinine measurement methods explain part of this variation. Further research is needed into clinical factors playing a role in decision-making of nephrologists when to start dialysis.

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Conflict of interest statement. None declared.

References

Determinants of eGFR at start of RRT in paediatric patients

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Abstract

Background. Few studies have investigated the determinants of glomerular filtration rate (GFR) in paediatric patients starting on dialysis or with a transplant.

Methods. Data were collected as part of the European Society of Paediatric Nephrology/European Renal Association–European Dialysis and Transplant Association registry from 14 European countries and referred to incident...