Analysis of data from the ERA-EDTA Registry indicates that conventional chronic kidney disease treatments do not reduce the need for renal replacement therapy in Autosomal Dominant Polycystic Kidney Disease

Edwin M. Spithoven*
Esther Meijer
Christoph Wanner
Frederic Collart
Damian G. Fogarty
Andries Hoitsma
Maurizio Postorino
Oscar Zurriaga

Anneke Kramer*
Bjarne Orskov
Fergus Caskey
Patrik Finne
Jaap W. Groothoff
Marie-Béatrice Nogier
Pietro Ravani
Kitty J. Jager
Ron T. Gansevoort

* Both authors contributed equally

Published in Kidney International
Reference: Kid Int. 2014;86(6): 1244-1252
ABSTRACT

Background
Autosomal dominant polycystic kidney disease (ADPKD) is a major cause of end-stage kidney failure, but is often identified early and therefore amenable to timely treatment. Interventions known to postpone the need for renal replacement therapy (RRT) in non-ADPKD patients have also been tested in ADPKD patients, but with inconclusive results. To help resolve this we determined changes in RRT incidence rates as an indicator for increasing effective renoprotection over time in ADPKD.

Methods
We analyzed data from the European Renal Association-European Dialyses and Transplant Association Registry on 315,444 patients starting RRT in 12 European countries between 1991 and 2010, grouped into four 5-year periods.

Results
Of them, 20,596 were due to ADPKD. Between the first and last period the mean age at onset of RRT increased from 56.6 to 58.0 years. The age- and gender-adjusted incidence rate of RRT for ADPKD increased slightly over the four periods from 7.6 to 8.3 per million population. No change over time was found in the incidence of RRT for ADPKD up to age 50, whereas in recent time periods the incidence in patients above the age of 70 clearly increased. Among countries there was a significant positive association between RRT take-on rates for non-ADPKD kidney disease and ADPKD.

Conclusion
Thus, the increased age at onset of RRT is most likely due to an increased access for elderly ADPKD patients or lower competing risk prior to the start of RRT rather than the consequence of effective emerging renoprotective treatments for ADPKD.
INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common heritable kidney disease, affecting approximately 1 in every 1000 subjects. Most affected subjects show progressive renal function decline and need renal replacement therapy (RRT) between their 40th and 70th year of age.

Over the past decades several treatment options have emerged to postpone the need for RRT in subjects with chronic kidney disease, such as strict blood pressure control, RAAS inhibition and low protein diets. These treatment options have also been tested in subjects with ADPKD with disappointing results. However, the results obtained in ADPKD studies should be interpreted with caution, since these studies were in general insufficiently powered to reach definitive conclusions. Furthermore, the ADPKD patients that were included were often still in the phase of their disease where renal function is relatively stable. In such patients it is difficult to study the renoprotective efficacy of interventions. Therefore, a conclusive answer to the question whether the conventional renoprotective regimens are effective in ADPKD patients is still lacking.

Interestingly, two observational studies have suggested that in ADPKD patients the average age of onset of end-stage renal disease has increased considerably during the last two decades. This finding has been interpreted as that effective renoprotective therapies have emerged for ADPKD, with especially males having achieved a better prognosis. However, these observational studies were performed in relatively small patient populations (513 and 693 patients, respectively) which may have led to publication bias.

It is surprising to note that the epidemiology of renal replacement therapy for ADPKD has seldom been studied, especially because ADPKD is one of the most common causes of end-stage renal disease. Given these considerations we used the European Renal Association - European Dialyses and Transplant Association (ERA-EDTA) Registry data to provide the largest epidemiological dataset on ADPKD yet. We used these data to study change in incidence rate of RRT, and average age and treatment modality at onset of RRT. The hypothesis of this study was that with a stable prevalence of ADPKD in the general population, change in incidence rates of RRT may provide indications whether renoprotective treatments have emerged for ADPKD during the last two decades.
METHODS

Data collection
This study was conducted using data of RRT patients participating in the ERA-EDTA Registry. Details of this study protocol have been published elsewhere.10 In summary, 24 national and regional registries from 12 countries within Europe are participating, covering a population of 208 million people. Individual patient data, including date of birth, sex, primary kidney disease, treatment modality history (hemodialysis, peritoneal dialysis and transplantation), and date and cause of death were derived from the national registries of Austria, Denmark, Finland, France, Greece, Romania, Sweden, the Netherlands and England, Wales, Northern Ireland, Scotland (the United Kingdom), and from the regional registries of Dutch and French-speaking Belgium, Calabria (Italy), Andalusia, Aragon, Asturias, Basque country, Cantabria, Castile and León, Castile-La Mancha, Catalonia, Extremadura, Galicia, and Valencian region (Spain). Additionally, we combined the individual and aggregated data, which were derived from Estonia, Latvia, Poland, Slovakia and Slovenia, for the incidence rate of RRT for ADPKD versus for non-ADPKD. Information on all RRT patients was used, except for Belgium, Spain (Cantabria, Castile and Leon and Castile-La Mancha) and the United Kingdom (except Scotland) from whom only information on patients >20 years of age was provided. As ADPKD patients rarely reach end-stage renal disease before this age, this limitation was not expected to influence results on prevalence of RRT for ADPKD. Registries from the following countries/regions provided complete information for all years within the study period: Andalusia (Spain), Austria, Basque country (Spain), Catalonia (Spain), Denmark, Finland, French-speaking Belgium, Greece, Sweden, Scotland, the Netherlands, and Valencia (Spain). For Belgium, Spain and the United Kingdom (except Scotland that provided complete data for the whole period), participation rates increased over time. Information on participation rates is shown in Supplementary Table 1.

Definition
Incidence of RRT was defined as the number of patients starting on any modality of RRT annually at day 1, whereby the type of modality on which they started was assessed at day 91. Incidence rate per million population (pmp) was calculated by dividing the observed count by the mid-year population. Primary renal disease for which RRT was started was coded using the ERA-EDTA coding system.11 Two ERA-EDTA primary renal disease codes can be used for the diagnosis of ADPKD: 40 (unspecified polycystic kidney disease) and 41 (polycystic kidney disease adult
type). Among countries, a substantial variation (0.2% to 2.7%) in incidence of code 40 was observed (see Supplementary Table 2). We combined the codes 40 and 41 for the definition ADPKD, because the incidence of non-ADPKD polycystic kidney disease is expected to be very low and unlikely to account for figures such as 2.7%.

Data analysis
The incidences of treatment modality of ADPKD patients treated with RRT were compared to similar study parameters in non-ADPKD patients (all other RRT patients). Incidence of RRT was studied in four consecutive 5-year periods (1991-1995, 1996-2000, 2001-2005, and 2006-2010). For each period, we calculated the incidence for ADPKD as the number of patients starting RRT annually in 5 subsequent years, divided by the sum of the total population in the same 5 years. The age and sex distribution of the 2005 EU27 population, as provided by Eurostat, was used to adjust for age and sex, to allow evaluation of trends in time and population differences among countries. Average data in figures and tables are calculated taking into account only data from registries/countries with complete follow-up during all four study periods, unless stated differently.

To investigate the association between incidences of RRT for ADPKD versus for non-ADPKD and to calculate corresponding p-values, we used weighted least squares regression analysis that takes country specific sample sizes into account. Regression analyses were carried out using SPSS version 20. To investigate the association between age and incidence of RRT, we plotted the number of ADPKD patients that started RRT per age category. We used t-tests and ANOVAs to study differences in mean age at start of RRT over time and between males and females.

For an earlier study, data were collected on the last serum creatinine assessed in the 0-4 weeks before the start of dialysis. The registries of Dutch-speaking and French-speaking Belgium, Valencia (Spain), Finland, Greece, Basilicata (Italy), Piedmont (Italy) and United Kingdom (Scotland) participated. Details of this study have been published elsewhere.

RESULTS

Incidence rate of RRT
Between 1991 and 2010 a total of 314,176 patients from 12 countries started RRT; of these patients 20,483 had ADPKD as cause of kidney failure and 293,693 patients other kidney diseases. 54% of ADPKD patients were male and 62% of non-
ADPKD patients. Over this time period the crude incidence rate of RRT for ADPKD increased from 6.9 to 8.4 pmp. Table 1 shows the international variation in the age- and sex-adjusted RRT incidence rate of ADPKD subjects, which is in the most recent period ranging from 5.3 per million of the population (pmp) in Romania to 10.0 pmp in Belgium. Figure 1 visualises these differences in RRT incidence rates for ADPKD geographically.

**Figure 1.** Incidence rate of renal replacement therapy (RRT) for ADPKD in member states of the EU27. Data are expressed per million of the population (pmp) and adjusted for age and sex to the 2005 EU27 population. Data are the average values for the time period 2006-2010.

**Trends in incidence rate of RRT**

Although, the relative contribution of ADPKD to the total incident RRT population decreased from 7.7 % in 1991-1995 to 6.1 % 2006-2010 (Supplementary Figure 1), the average age- and gender- adjusted incidence rate has increased by 9.2% from 7.6 pmp in 1991-1995 to 8.3 pmp in 2006-2010 (Table 1). Differences in trends were
Incidence of RRT for ADPKD

observed among countries, with the Netherlands and Italy showing a slight decrease and other countries showing an increase over time.

Table 1. Incidence rate of renal replacement therapy for ADPKD at day 1, and incidence rate of dialysis (hemodialysis and peritoneal dialysis) or kidney transplantation as primary modality of RRT at day 91 (middle and lower panel, respectively). Rates are standardised for age and sex to the 2005 EU27 population, and expressed per million population (pmp).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All RRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>6.8</td>
<td>8.1</td>
<td>8.0</td>
<td>7.3</td>
<td>+7.4</td>
</tr>
<tr>
<td>Belgium*</td>
<td>6.9</td>
<td>9.4</td>
<td>8.9</td>
<td>10.0</td>
<td>NA</td>
</tr>
<tr>
<td>Denmark</td>
<td>7.2</td>
<td>8.0</td>
<td>8.2</td>
<td>8.1</td>
<td>+12.5</td>
</tr>
<tr>
<td>Finland</td>
<td>6.5</td>
<td>8.5</td>
<td>7.8</td>
<td>7.1</td>
<td>+9.2</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>6.4</td>
<td>7.4</td>
<td>8.1</td>
<td>7.6</td>
<td>+18.8</td>
</tr>
<tr>
<td>Italy, Calabria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td></td>
<td></td>
<td></td>
<td>7.4</td>
<td>-2.7</td>
</tr>
<tr>
<td>Spain</td>
<td>9.6</td>
<td>10.4</td>
<td>9.3</td>
<td>9.2</td>
<td>NA</td>
</tr>
<tr>
<td>Sweden</td>
<td>8.6</td>
<td>8.7</td>
<td>8.7</td>
<td>9.1</td>
<td>+5.8</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>7.6</td>
<td>7.2</td>
<td>7.7</td>
<td>7.1</td>
<td>-6.6</td>
</tr>
<tr>
<td>United Kingdom*</td>
<td>5.9</td>
<td>6.4</td>
<td>6.4</td>
<td>7.1</td>
<td>NA</td>
</tr>
<tr>
<td>All countries*</td>
<td>7.6</td>
<td>8.5</td>
<td>8.5</td>
<td>8.3</td>
<td>+9.2</td>
</tr>
<tr>
<td>Dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>6.5</td>
<td>7.5</td>
<td>7.5</td>
<td>6.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Belgium*</td>
<td>6.6</td>
<td>8.6</td>
<td>8.5</td>
<td>9.2</td>
<td>NA</td>
</tr>
<tr>
<td>Denmark</td>
<td>6.0</td>
<td>7.2</td>
<td>7.4</td>
<td>7.3</td>
<td>+21.7</td>
</tr>
<tr>
<td>Finland</td>
<td>6.0</td>
<td>8.4</td>
<td>7.6</td>
<td>6.9</td>
<td>+15.0</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td>7.9</td>
<td>NA</td>
</tr>
<tr>
<td>Greece</td>
<td>6.3</td>
<td>7.4</td>
<td>7.8</td>
<td>7.3</td>
<td>+15.9</td>
</tr>
<tr>
<td>Italy, Calabria</td>
<td></td>
<td></td>
<td></td>
<td>6.9</td>
<td>-5.4</td>
</tr>
<tr>
<td>Romania</td>
<td></td>
<td></td>
<td></td>
<td>5.0</td>
<td>NA</td>
</tr>
<tr>
<td>Spain</td>
<td>9.3</td>
<td>10.0</td>
<td>8.9</td>
<td>8.5</td>
<td>NA</td>
</tr>
<tr>
<td>Sweden</td>
<td>7.5</td>
<td>7.8</td>
<td>7.5</td>
<td>7.8</td>
<td>+4.0</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>7.3</td>
<td>6.9</td>
<td>7.2</td>
<td>6.0</td>
<td>-17.8</td>
</tr>
<tr>
<td>United Kingdom*</td>
<td>5.5</td>
<td>5.9</td>
<td>5.8</td>
<td>5.9</td>
<td>NA</td>
</tr>
<tr>
<td>All countries*</td>
<td>7.2</td>
<td>8.0</td>
<td>8.0</td>
<td>7.5</td>
<td>+4.2</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.6</td>
<td>+200</td>
</tr>
<tr>
<td>Belgium*</td>
<td>0.3</td>
<td>0.5</td>
<td>0.2</td>
<td>0.5</td>
<td>NA</td>
</tr>
<tr>
<td>Denmark</td>
<td>0.9</td>
<td>0.6</td>
<td>0.5</td>
<td>0.7</td>
<td>-22.2</td>
</tr>
<tr>
<td>Finland</td>
<td>0.4</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>-75.0</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td>1.3</td>
<td>NA</td>
</tr>
<tr>
<td>Greece</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
<td>0.2</td>
<td>NA</td>
</tr>
<tr>
<td>Italy, Calabria</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
<td>NA</td>
</tr>
<tr>
<td>Romania</td>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
<td>NA</td>
</tr>
<tr>
<td>Spain</td>
<td>0.0</td>
<td>0.3</td>
<td>0.3</td>
<td>0.5</td>
<td>NA</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.9</td>
<td>0.7</td>
<td>0.9</td>
<td>1.1</td>
<td>+22.2</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>0.3</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
<td>+233</td>
</tr>
<tr>
<td>United Kingdom*</td>
<td>0.1</td>
<td>0.4</td>
<td>0.5</td>
<td>1.1</td>
<td>NA</td>
</tr>
<tr>
<td>All countries*</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.7</td>
<td>+133</td>
</tr>
</tbody>
</table>

NA, not applicable or available (due to change in coverage over time)

*Coverage of the general population by the renal registry increasing over time, see for details Supplementary Table 1.

* Average of countries with complete coverage during all 4 study periods.

Age, sex and eGFR at start of RRT

Table 2 shows country specific data and the mean age at onset of RRT for ADPKD patients for each of the four study periods. We observed an increase in the mean age at start of RRT from 56.6 to 58.0 years (p<0.001). The mean age at onset of RRT was significantly higher in women than in men in all time periods (p<0.001). From 1991 to 2010 the mean age increased on average by 1.4 year in men and by 1.5 year women. In non-ADPKD patients, the mean age at start RRT increased from 57.6 to 64.7 years (p<0.001). Over time the age-adjusted male/female ratio of RRT incidence for ADPKD has remained stable (1.19, 1.28, 1.20 and 1.20, respectively). The additional analyses of eGFR data collected for an earlier study showed for the subgroup of ADPKD patients that the average estimated glomerular filtration rate (eGFR) in ADPKD patients at onset of dialysis increased only slightly (by 0.6 ml/min/1.73m², from 7.2 to 7.8 ml/min/1.73m²) in 2003 compared to 1999.

Table 2. Mean age (in years) of ADPKD and non-ADPKD patients starting renal replacement therapy, country specific data and average (for which only countries are taken into account with complete coverage during all 4 study periods.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All RRT for ADPKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>57.4</td>
<td>59.1</td>
<td>58.6</td>
<td>59.5</td>
</tr>
<tr>
<td>Belgium*</td>
<td>58.1</td>
<td>58.2</td>
<td>59.5</td>
<td>58.9</td>
</tr>
<tr>
<td>Denmark</td>
<td>55.6</td>
<td>58.1</td>
<td>60.0</td>
<td>59.9</td>
</tr>
<tr>
<td>Finland</td>
<td>54.0</td>
<td>57.3</td>
<td>57.3</td>
<td>58.3</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td>58.9</td>
</tr>
<tr>
<td>Greece</td>
<td>55.1</td>
<td>56.7</td>
<td>58.1</td>
<td>58.9</td>
</tr>
<tr>
<td>Italy, Calabria</td>
<td></td>
<td>61.5</td>
<td>59.8</td>
<td>60.2</td>
</tr>
<tr>
<td>Romania</td>
<td></td>
<td></td>
<td></td>
<td>55.9</td>
</tr>
<tr>
<td>Spain*</td>
<td>56.8</td>
<td>57.6</td>
<td>58.0</td>
<td>57.6</td>
</tr>
<tr>
<td>Sweden</td>
<td>58.7</td>
<td>57.9</td>
<td>60.6</td>
<td>58.2</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>56.5</td>
<td>56.2</td>
<td>56.7</td>
<td>58.4</td>
</tr>
<tr>
<td>United Kingdom*</td>
<td>54.9</td>
<td>55.5</td>
<td>56.5</td>
<td>55.5</td>
</tr>
<tr>
<td>All countries*</td>
<td><strong>56.6</strong></td>
<td><strong>57.4</strong></td>
<td><strong>58.2</strong></td>
<td><strong>58.0</strong></td>
</tr>
<tr>
<td>- Female</td>
<td>57.1</td>
<td>58.4</td>
<td>58.7</td>
<td>58.6</td>
</tr>
<tr>
<td>- Male</td>
<td>56.1</td>
<td>56.5</td>
<td>57.7</td>
<td>57.5</td>
</tr>
<tr>
<td>All RRT for non-ADPKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All countries*</td>
<td><strong>57.6</strong></td>
<td><strong>60.8</strong></td>
<td><strong>63.5</strong></td>
<td><strong>64.7</strong></td>
</tr>
<tr>
<td>- Female</td>
<td>57.9</td>
<td>61.4</td>
<td>64.1</td>
<td>62.5</td>
</tr>
<tr>
<td>- Male</td>
<td>57.3</td>
<td>60.4</td>
<td>63.1</td>
<td>64.5</td>
</tr>
</tbody>
</table>

* Coverage of the general population by the renal registry increasing over time, see for details Supplementary Table 1.
* Average of countries with complete coverage during all 4 periods.

Trends in incidence rate of RRT by age

Figure 2 shows the incidence rate of RRT for ADPKD per age group for each of the four study periods. Importantly, there was no change in the incidence rate in subjects up to 50 years of age. Only the incidence rate in subjects older than 70 years of age increased. Over the four study periods the incidence rate in subjects
younger than 30 years remained stable at less than 0.5 pmp (Supplementary Figure 2). Similarly, the incidence rates remained fairly stable or changed minimally in patients in their third to sixth decade of life: 3.0 to 3.1 pmp, 11.9 to 12.8 pmp, 19.0 to 18.8 pmp and 17.0 to 17.5 pmp, respectively, when comparing the time periods 1991-1995 and 2006-2010. In contrast for the patients aged 70-79 and above 80 years, the incidence has increased from 14.3 to 17.3 pmp and from 3.0 to 9.2 pmp. In both age groups a plateau was reached during the last study period (2006-2010) (Supplementary Figure 2).

Figure 2. Incidence rate of renal replacement therapy for ADPKD per age group. Data are expressed per million of the age related population (pmarp) and given for four consecutive study periods.

**Incidence and treatment modality at start of RRT in ADPKD versus non-ADPKD**

Figure 3 shows the association between the incidence rates of RRT for ADPKD and for non-ADPKD patients in the time period 2006-2010. It indicates that countries with a high take-on rate for RRT in general, also have a high take-on rate for ADPKD patients. In an additional analysis including only patients older than 70 years of age also a positive association was found between ADPKD and non-ADPKD patients ($R^2 = 0.651$, $\beta = 0.02$ (95% CI 0.01 - 0.02, $p=0.002$). This indicates that countries with a high take-on rate for elderly non-ADPKD patients also have a high take-on rate for elderly ADPKD patients. During the four study periods, the age- and sex-adjusted percentage of ADPKD patients that started RRT on hemodialysis decreased from
Table 3. Trends over time in treatment modality on which ADPKD patients start renal replacement therapy. Percentages are standardized for age and sex to the 2005 EU27 population.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADPKD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>73.6</td>
<td>77.3</td>
<td>74.2</td>
<td>70.1</td>
<td>-4.8</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>22.4</td>
<td>19.3</td>
<td>21.5</td>
<td>21.6</td>
<td>-3.6</td>
</tr>
<tr>
<td>Kidney transplant recipients</td>
<td>3.9</td>
<td>3.4</td>
<td>4.4</td>
<td>8.1</td>
<td>+108</td>
</tr>
<tr>
<td>- Living donor</td>
<td>1.3</td>
<td>1.7</td>
<td>2.8</td>
<td>5.6</td>
<td>+319</td>
</tr>
<tr>
<td>- Deceased donor</td>
<td>2.4</td>
<td>1.5</td>
<td>1.5</td>
<td>2.3</td>
<td>-1.7</td>
</tr>
<tr>
<td>- Unknown donor</td>
<td>0.2</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2</td>
<td>+8.7</td>
</tr>
<tr>
<td><strong>Non-ADPKD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>74.9</td>
<td>77.2</td>
<td>79.9</td>
<td>79.4</td>
<td>+6.0</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>22.5</td>
<td>20.5</td>
<td>17.7</td>
<td>16.7</td>
<td>-25.8</td>
</tr>
<tr>
<td>Kidney transplant recipients</td>
<td>2.6</td>
<td>2.3</td>
<td>2.3</td>
<td>3.8</td>
<td>+46.2</td>
</tr>
<tr>
<td>- Living donor</td>
<td>1.1</td>
<td>1.2</td>
<td>1.4</td>
<td>2.6</td>
<td>+130</td>
</tr>
<tr>
<td>- Deceased donor</td>
<td>1.2</td>
<td>1.0</td>
<td>0.8</td>
<td>1.0</td>
<td>-17.7</td>
</tr>
<tr>
<td>- Unknown donor</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

For these data only countries were taken into account with complete coverage during all 4 periods. 

73.6 to 70.1% from 1991 to 2010 (Table 3), whereas peritoneal dialysis remained stable at approximately 22% and transplantation increased from 3.9% to 8.1%. Figure 4 shows that ADPKD patients start RRT as often on peritoneal dialysis as non-ADPKD patients. A clear difference is noted for kidney transplantation, which
Figure 4: Treatment modality at day 91 after starting renal replacement therapy comparing ADPKD versus non-ADPKD patients. Patients on hemodialysis (left panel), peritoneal dialysis (middle panel) kidney transplant recipients (right panel) as percentage of the incident renal replacement therapy population. Data are the average of the period 2006 through 2010 and adjusted for age and sex to the distribution of the EU27 population in 2005. The size of marker denotes the size of the general population under study. Abbreviations AT, Austria; BE, Belgium; DK, Denmark; ES, Spain; FI, Finland; FR, France; GR, Greece; IT, Italy, Calabria; NL, The Netherlands; RO, Romania; SE, Sweden; UK, United Kingdom.
is more often the initial treatment modality in ADPKD than in non-ADPKD patients. A similar trend is observed for patients receiving kidneys transplantation from living donors as well as deceased donors (Supplementary Figure 3).

**DISCUSSION**

This study shows that the incidence rate of RRT and the age at onset of RRT for ADPKD have slightly increased. Importantly, for ADPKD patients up to 50 years of age the RRT incidence rate expressed per million of the age related population has remained stable, whereas at older age an increase was observed. Furthermore, a positive association was found between the RRT incidence rate for ADPKD and for non-ADPKD patients. We interpret these findings as that this may be due to more elderly starting RRT, rather than that this was the consequence of effective renoprotective treatments having emerged for ADPKD.

Two observational studies have addressed this issue previously. Data from the University of Colorado Health Sciences Center suggested that recent ADPKD patients have a significant slower rate of ADPKD progression. In this study the average median survival time to RRT was investigated in two cohorts of patients, (i.e. 1985 - 1992 versus 1992 - 2001). The average age at start of RRT increased substantially for both male and female patients (from 53 to 63 years, and from 57 to 61 years, respectively). A Danish population study showed that the incidence rate increased from 6.45 pmp to 7.59 pmp in a period of 17 years (1990-2007) and that the age at starting RRT also increased (from 55.9 to 60.6 years). The former study was relatively small with only 513 ADPKD patients included, and the baseline characteristics of the two studied cohorts differed, suggesting that the later cohort may have had a milder form of ADPKD. The Danish study reported country-wide data. However, given the fact that ADPKD has a population prevalence of 1:1000 and that ADPKD is a slowly progressive disease, the number of ADPKD patients that started RRT during the study period was still relatively low (n=693), and consequently did not allow us to reliably report RRT incidence data per age group. In line with the aforementioned literature, the present study showed that the age at onset RRT has increased during the last decades, albeit considerably less (from 56.6 to 58.0 years) than reported previously. Of note, a recent study from the Catalan registry that is included in the present report showed no change in age at onset of RRT. Furthermore, we also observed that the age- and sex-adjusted RRT incidence rate increased for ADPKD by 9.2% during the four study periods. Importantly, we established that the incidence rate of RRT for ADPKD remained
Incidence of RRT for ADPKD

stable up to 50 years of age and increased only in subjects aged 70 years and older.

The combination of an increase in incidence rate of RRT and an increase in age at onset of RRT may be interpreted in various ways. This combination may suggest that overall as well as kidney prognosis has improved in ADPKD patients. However, it may also be that specifically more elderly are starting RRT nowadays. If effective renoprotective treatment had emerged during the last two decades in ADPKD, it would be expected that the entire curve of the incidence rate per million of the age related population would have shifted to the right for the most recent study periods, because renoprotective treatments would affect all age groups. However, we found no change in the incidence rate up to 50 years of age. This age group is thought to reflect the true incidence rate of kidney failure. Younger patients are less subject to variation in access and referral to RRT than older patients.\(^9\) Furthermore, in this age group the mortality as competing risk for start of RRT is low. Therefore, we derive from our data that no effective renoprotective therapies have emerged for ADPKD. This may seem to be in contrast to both aforementioned observational studies.\(^8,9\) However, because of the limited size of their included populations it was not possible in these studies to investigate incidence data per age group, as in the present study. We found that only after the age of 70 years the RRT incidence rate curve has shifted to the right, indicating that in this age group, and especially in the very elderly (≥80 years), RRT incidence increased. This is compatible with the widespread clinical notion that nowadays more elderly start RRT due to changes in RRT take-on policies and due to a reduction in the competing risk of mortality. Our interpretation that no effective renoprotective treatment has emerged for ADPKD is further supported by the positive association between incidence rate of RRT for ADPKD versus non-ADPKD. Countries with a high overall RRT take-on rate also have a higher RRT take-on rate for ADPKD. Of note, recent studies suggest that vasopressin V2 receptor antagonists and somatostatin analogues ameliorate the rate of decline in kidney function in ADPKD patients. However, these treatments are not available for clinical use in ADPKD patients yet.\(^16,17\)

Theoretically there may be several potential explanations as to why the incidence rate of RRT has not changed in younger ADPKD patients, despite renoprotection that may have been obtained in this age group. First, it could be that survival in young ADPKD patients before onset of RRT has improved. Clinical experience and scant literature indicate, however, that mortality in ADPKD patients before the age of 55 years is very low,\(^16,18-20\) making it unlikely that this would have biased our results.
Second, the average eGFR at which RRT is initiated may have increased, leading to an earlier start of RRT. The analysis of eGFR data at start of RRT derived from a previous ERA-EDTA registry study showed that in ADPKD patients indeed the average eGFR at onset of dialysis was higher in 2003 than in 1999. However, this difference was small (0.6 ml/min/1.73m²), whereas the rate of eGFR loss in ADPKD is between 3 and 6 ml/min/1.73m² per year. These data indicate that a higher eGFR at start of RRT translate into an earlier start of RRT of maximum 0.5 year, which would not substantially influence our data in Figure 2. Third, there may be relatively more ADPKD subjects in the general population at present. Unfortunately, reliable data on ADPKD population prevalence over time are unavailable. Since ADPKD is a hereditary disease of which most affected subjects know from their relatives that it is associated with an unfavorable prognosis, it may be expected that given the widespread availability of contraceptives nowadays family size remained the same or has become smaller rather than increased. Therefore, we consider it unlikely that an increase in ADPKD population prevalence will have biased our interpretation of the findings. Finally, in the past ADPKD may have been underdiagnosed. Given the family history of these patients, and the ease with which this diagnosis can clinically be made using imaging techniques that have been widely available the last 20 years, also this potential explanation seems unlikely.

Importantly, with these data we do not imply that strict blood pressure control, ACE inhibition, statins, and low salt and low protein diets should not be prescribed. Although these regimens may not affect the rate of kidney disease progression in ADPKD, they have shown to reduce cardiovascular co-morbidity and mortality in patients on RRT as well as before RRT. It should be acknowledged though that this has not been investigated in specifically ADPKD patients. However, better survival of ADPKD patients prior to start of RRT may explain at least in part the increase in RRT incidence rate in elderly ADPKD patients that we observed in the present study. Such an increase in survival of pre-ESRD ADPKD patients has indeed been reported by others.

Some other findings in our study are worth to be mentioned. The RRT incidence rate for ADPKD in Europe (8.3 pmp in 2006-2010) is equivalent to that in the United States (8.1 pmp in 2010), but higher than in Japan (4.8 pmp in 2000). These registries report on sufficiently large datasets to reliably suggest that racial differences in ADPKD prevalence or rate of disease progression may exist. During the study period, the proportion of ADPKD patients of all patients starting RRT has decreased. Our data indicate that this is due to an increase in incidence of RRT.
Incidence of RRT for ADPKD

for non-ADPKD. The adjusted male/female RRT incidence ratio for ADPKD has remained stable in our population at approximately 1.20 during the study period, which is comparable to the male/female RRT incidence ratio for ADPKD in Japan (1.32)\(^2\) and the USA (1.2-1.3).\(^2\) This confirms previous studies that suggested that male ADPKD patients have a worse prognosis with respect to renal outcome.\(^2\,2^4\)

During the last two decades, the distribution pattern of the different modalities at which ADPKD patients started RRT has changed. ADPKD patients received more kidney transplantations than non-ADPKD patients from both living and deceased donors. This may be due to increased awareness and willingness of non-affected family members to donate a kidney. It may also be that ADPKD patients in general have less co-morbidity and are therefore more easily accepted on transplant waiting lists and because they are often diagnosed many years before ESRD and thus have more time for transplant preparation.

This study has a number of limitations. The ERA-EDTA Registry does not contain information on actual use of possible renoprotective treatments. However, it is generally acknowledged that nowadays ADPKD patients are better treated for hypertension and that a larger proportion receives ACE-inhibition.\(^2^1,2^5\)

Not all European Union countries participated and complete follow-up was not available for each registry during all time periods. For the purpose of this study, however, this was not essential, because the conclusions are based on those registries that had complete follow-up over time. This study still covers 42% of the inhabitants of the European Union representing more than 200 million people, and reports therefore on the largest epidemiological dataset on ADPKD thus far. Another strength is that we investigated not only overall RRT incidence rates, as previous studies did, but also the incidence per RRT treatment modality and compared data obtained in ADPKD to non-ADPKD patients.

In summary, this analysis shows that for ADPKD the incidence of RRT, as well as the age at which RRT is started, have increased slightly. ADPKD RRT incidence rates were stable in younger subjects, but increased in elderly. We interpret these findings as that this may be due to more elderly having been selected to start RRT or to a decrease in mortality of older patients prior to reaching ESRD rather than as effective renoprotective treatments having emerged for ADPKD.

DISCLOSURE

All authors declare no conflict of interest.
ACKNOWLEDGEMENTS

We thank the patients and the staff of all the dialysis and transplant units who contributed data via their national or regional renal registries. Furthermore, we gratefully acknowledge the following persons for their contribution to the work of the ERA-EDTA Registry: R. Kramar (Austrian Dialysis and Transplant Registry [OEDTR]); B. de Moor, H. Augustijn, and J. de Meester (Dutch-Belgian Nephrology Registry [NBVN]); J-M. des Grottes and F. Collart (French-speaking Belgium Registry); J.G. Heaf (Danish Society of Nephrology [DNSL]); P. Castro de la Nuez and M.A. Pérez Valdivia (Andalusian Kidney Transplant Registry [SICATA]); J.I. Sanchez Miret and J.M. Abad Diez (Aragon Renal Registry); R. Alonso de la Torre, J.R. Quiros, and E Sanchez (Asturias Renal Registry [RERCA]); Á. Magaz, J. Aranzabal, M. Rodrigo, and I. Moina (Basque Country Renal Registry); M. Arias Rodríguez, and O. García Ruiz (Cantabrian Renal registry); E. Arcos, J. Comas, and P.A. Montserrat (Catalan Renal Registry [RMRC] and Catalan Transplant Organisation [OCATT]); G. Gutiérrez Ávila and I. Moreno Alía (Castile-La Mancha Renal Registry); R. González and C. García-Renedo (Castile and León Renal Registry); J.M. Ramos Aceitero and M.A. García Bazaga (Extremadura Renal Registry); E. Bouzas-Camaño and J. Sánchez-Ibáñez (Galicia Renal Registry); M. Ferrer Alamar (Registro de Enfermos Renales de la Comunidad Valenciana [REMRENAL]); C. Grönhagen-Riska (Finnish Registry for Kidney Diseases); M. Lassalle (French Renal Epidemiology and Information Network [REIN] registry); G.A. Ioannidis (Greek national Renal Registry); Calabrian Renal Registry; A. Hemke (Dutch End-Stage Renal Disease Registry [RENINE]); G. Mircescu, L. Garneata, and E. Podgoreanu (Romanian Renal Registry); K.G. Prütz, L. Bäckman, M. Evans, S. Schön, M. Stendahl, and B. Rippe [Swedish Renal Registry (SNR)]; All the staff of the UK Renal Registry and of the renal units submitting data; and The staff of the Scottish Renal Registry and all of the Scottish renal units for their participation in the data collection. The ERA–EDTA Registry is funded by the ERA–EDTA.
Incidence of RRT for ADPKD

ERA-EDTA Registry collaborators: Aresté, N.¹, Arias M.², Couchoud C.³


WGIKD Steering Committee: Antignac C.¹⁸,¹⁹, Bindels R.²⁰, Chauveau D.⁵, Devuyst O.⁶, Emma F.²¹, Gansevoort R.T.⁹, Maxwell P.H.²², Ong A.C.¹¹, Remuzzi G.¹³, Ronco P.²³ Schaefer F.²⁴. WGIKD is the acronym for Working Group on Inherited Kidney Disease. The WGIKD is supported by the ERA-EDTA.

¹ Department of Nephrology, University Hospital Virgen Macarena. Seville, Spain
² Department of Nephrology, Hospital Universitario Marqués de Valdecilla, Santander, Spain
³ REIN Registry, Agence de la Biomedecine, Saint Denis La Plaine, France
⁴ Charité University Hospital, Berlin, Germany
⁵ Centre de référence des maladies rénales rares, CHU Rangueil, Toulouse, France
⁶ Institute of Physiology, Zurich Centre for Integrative Human Physiology, University of Zurich, Zurich, Switzerland
⁷ Division of Nephrology, Istanbul School of Medicine, Istanbul, Turkey
⁸ Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Germany
⁹ Department of Nephrology, University Medical Center Groningen (UMCG), University of Groningen, Groningen, the Netherlands
¹⁰ Renal Division, Freiburg University Clinic, Freiburg, Germany
¹¹ Academic Nephrology Unit, Faculty of Medicine, Dentistry and Health, University of Sheffield, Sheffield, United Kingdom
¹² Division of Nephrology, UCL Medical School, Brussels, Belgium
¹³ Clinical Research Center for Rare Diseases “Aldo & Cele Daccò”, IRCCS - Istituto di Ricerche Farmacologiche “Mario Negri” and Unit of Nephrology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
¹⁴ Dept. Nephrology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain
¹⁵ Academic Department of Medical Genetics, University of Cambridge School of Clinical Medicine, Cambridge, the United Kingdom
¹⁶ Department of Nephrology, 1st Faculty of Medicine and General Faculty Hospital 1st Faculty of Medicine, Charles University Prague, Czech Republic
¹⁷ Division of Nephrology, University Hospital, Zurich, Switzerland
18 Département de Génétique, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France
19 Inserm U983 and Université Paris Descartes, Institut Imagine, Sorbonne Paris Cité, Paris, France
20 Department of Physiology, Radboud University Nijmegen, Nijmegen, The Netherlands
21 Division of Nephrology and Dialysis, Department of Nephrology and Urology, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy
22 University of Cambridge School of Clinical Medicine, Addenbrooke’s Hospital, Cambridge, United Kingdom
23 Sorbonne Universités, UPMC Univ Paris 06, UMR_S 1155, F-75005, Paris, France
24 Division of Paediatric Nephrology, Centre for Paediatric and Adolescent Medicine, University Hospital of Heidelberg, Heidelberg, Germany
REFERENCES

Supplementary Figure 1. Trends in relative contribution of ADPKD to all incident RRT (%). Data are expressed as percentage of the overall population starting renal replacement therapy. Abbreviations: AT, Austria; BE, Belgium; DK, Denmark; ES, Spain; FI, Finland; FR, France; GR, Greece; IT, Italy, Calabria; NL, The Netherlands; RO, Romania; SE, Sweden; UK, United Kingdom.
* Coverage of the general population by the renal registry increasing over time, see for details Supplementary Table 1.
+ Average of countries with complete coverage during all 4 study periods.
**Supplementary Figure 2.** Incidence rate of renal replacement therapy for ADPKD per study period. Data are expressed per million of the age related population (pmarp) and given per age group.
Supplementary Figure 3. Treatment modality at day 91 after starting renal replacement therapy comparing ADPKD versus non-ADPKD patients. Patients receiving a kidney transplant from a living donor (upper panel) or deceased donor (lower panel) as percentage of the overall incident renal replacement therapy population. Data are the average of the period 2006 through 2010 and adjusted for age and sex to the distribution of the 2005 EU27 population. The size of marker denotes the size of the general population under study. Abbreviations AT, Austria; BE, Belgium; DK, Denmark; ES, Spain; FI, Finland; FR, France; GR, Greece; IT, Italy, Calabria; NL, The Netherlands; RO, Romania; SE, Sweden; UK, United Kingdom.
### Supplementary Table 1. Country coverage of RRT information over time (expressed as percentage of the whole population per country of which such information is available)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Belgium^</td>
<td>42.1</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Denmark</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Estonia</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td>61.2</td>
</tr>
<tr>
<td>Greece</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Italy</td>
<td>3.6</td>
<td>3.5</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td></td>
<td></td>
<td></td>
<td>94</td>
</tr>
<tr>
<td>Portugal</td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Romania</td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Slovakia</td>
<td></td>
<td></td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>Slovenia</td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Spain</td>
<td>45.8^</td>
<td>53.1^</td>
<td>65.3^</td>
<td>73.2^</td>
</tr>
<tr>
<td>Sweden</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>United Kingdom^</td>
<td>8.8</td>
<td>35.6</td>
<td>77.0</td>
<td>98.5</td>
</tr>
</tbody>
</table>

^A First cohort only French-speaking Belgium participates;
^B Represents Andalusia, Basque country, Catalonia and Valencian region;
^C Represents ^B and Asturias Cantabria;
^D Represents ^C and Aragon, Castile and León, Castile-La Mancha and Extremadura;
^E Represents ^D and Galicia.
^F In the first cohort only Scotland participates.

### Supplementary Table 2. Incidence of RRT for the ERA-EDTA codes 40 (unspecified polycystic kidney disease) and 41 (polycystic kidney disease adult type) expressed as percentage of all incident RRT patients.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>2.7</td>
<td>3.2</td>
<td>1.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Belgium^</td>
<td>0.7</td>
<td>5.8</td>
<td>0.8</td>
<td>5.7</td>
</tr>
<tr>
<td>Denmark</td>
<td>0.6</td>
<td>7.7</td>
<td>0.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Finland</td>
<td>0.3</td>
<td>9.0</td>
<td>0.5</td>
<td>9.2</td>
</tr>
<tr>
<td>France</td>
<td>0.3</td>
<td>6.7</td>
<td>0.3</td>
<td>5.5</td>
</tr>
<tr>
<td>Greece</td>
<td>0.3</td>
<td>6.7</td>
<td>0.3</td>
<td>5.5</td>
</tr>
<tr>
<td>Italy, Calabria</td>
<td>0.2</td>
<td>5.4</td>
<td>0.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Romania</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>0.5^</td>
<td>8.3^</td>
<td>0.4^</td>
<td>7.4^</td>
</tr>
<tr>
<td>Sweden</td>
<td>2.4</td>
<td>5.0</td>
<td>1.5</td>
<td>5.3</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1.4</td>
<td>7.0</td>
<td>1.1</td>
<td>6.1</td>
</tr>
<tr>
<td>United Kingdom^</td>
<td>0.2</td>
<td>6.9</td>
<td>0.3</td>
<td>6.5</td>
</tr>
</tbody>
</table>

^A First cohort only French-speaking Belgium participates;
^B Represents Andalusia, Basque country, Catalonia and Valencian region;
^C Represents ^B and Asturias Cantabria;
^D Represents ^C and Aragon, Castile and León, Castile-La Mancha and Extremadura;
^E Represents ^D and Galicia.
^F In the first cohort only Scotland participates.