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## Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival - an analysis of data from the ERA-EDTA Registry

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**Abstract:** **BACKGROUND:** Autosomal dominant polycystic kidney disease (ADPKD) is the fourth most common renal disease requiring renal replacement therapy (RRT). Still, there are few epidemiological data on the prevalence of, and survival on RRT for ADPKD. **METHODS:** This study used data from the ERA-EDTA Registry on RRT prevalence and survival on RRT in 12 European countries with 208 million inhabitants. We studied four 5-year periods (1991-2010). Survival analysis was performed by the Kaplan-Meier method and by Cox proportional hazards regression. **RESULTS:** From the first to the last study period, the prevalence of RRT for ADPKD increased from 56.8 to 91.1 per million population (pmp). The percentage of prevalent RRT patients with ADPKD remained fairly stable at 9.8%. Two-year survival of ADPKD patients on RRT (adjusted for age, sex and country) increased significantly from 89.0 to 92.8%, and was higher than for non-ADPKD subjects. Improved survival was noted for all RRT modalities: haemodialysis [adjusted hazard ratio for mortality during the last versus first time period 0.75 (95% confidence interval 0.61-0.91), peritoneal dialysis 0.55 (0.38-0.80) and transplantation 0.52 (0.32-0.74)]. Cardiovascular mortality as a proportion of total mortality on RRT decreased more in ADPKD patients (from 53 to 29%), than in non-ADPKD patients (from 44 to 35%). Of note, the incidence rate of RRT for ADPKD remained relatively stable at 7.6 versus 8.3 pmp from the first to the last study period, which will be discussed in detail in a separate study. **CONCLUSIONS:** In ADPKD patients on RRT, survival has improved markedly, especially due to a decrease in cardiovascular mortality. This has led to a considerable increase in the number of ADPKD patients being treated with RRT.

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# Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival—an analysis of data from the ERA-EDTA Registry

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## ABSTRACT

**Background.** Autosomal dominant polycystic kidney disease (ADPKD) is the fourth most common renal disease requiring renal replacement therapy (RRT). Still, there are few epidemiological data on the prevalence of, and survival on RRT for ADPKD.

**Methods.** This study used data from the ERA-EDTA Registry on RRT prevalence and survival on RRT in 12 European

countries with 208 million inhabitants. We studied four 5-year periods (1991–2010). Survival analysis was performed by the Kaplan–Meier method and by Cox proportional hazards regression.

**Results.** From the first to the last study period, the prevalence of RRT for ADPKD increased from 56.8 to 91.1 per million population (pmp). The percentage of prevalent RRT patients with ADPKD remained fairly stable at 9.8%. Two-year survival of ADPKD patients on RRT (adjusted for age, sex and

country) increased significantly from 89.0 to 92.8%, and was higher than for non-ADPKD subjects. Improved survival was noted for all RRT modalities: haemodialysis [adjusted hazard ratio for mortality during the last versus first time period 0.75 (95% confidence interval 0.61–0.91), peritoneal dialysis 0.55 (0.38–0.80) and transplantation 0.52 (0.32–0.74)]. Cardiovascular mortality as a proportion of total mortality on RRT decreased more in ADPKD patients (from 53 to 29%), than in non-ADPKD patients (from 44 to 35%). Of note, the incidence rate of RRT for ADPKD remained relatively stable at 7.6 versus 8.3 pmp from the first to the last study period, which will be discussed in detail in a separate study.

**Conclusions.** In ADPKD patients on RRT, survival has improved markedly, especially due to a decrease in cardiovascular mortality. This has led to a considerable increase in the number of ADPKD patients being treated with RRT.

**Keywords:** ADPKD, epidemiology, prevalence, survival, renal replacement therapy

## INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. It affects ~1 in every 1000 subjects of the general population [1]. The disease is characterized by progressive cyst formation, especially in the kidneys, leading to massive kidney enlargement, pain and haematuria. Most ADPKD subjects show progressive renal function decline and ~70% develop end-stage renal disease **between** their fourth and seventh decade of life [2–4]. ADPKD occurs worldwide and in all races [5], and it is generally assumed that this patient group accounts for around 10% of all subjects who are dependent on renal replacement therapy (RRT). However, differences in prevalence between regions have been suggested [6].

The choice of renal replacement modality is dependent on several factors, including patient choice, physicians' advice and resource availability. For the last 20 years, three RRT modalities have been available; haemodialysis, peritoneal dialysis and kidney transplantation. In ADPKD, peritoneal dialysis may be complicated by an increased prevalence of abdominal wall hernias and lower dialysis efficiency because of reduced abdominal space secondary to the enlarged kidneys and liver [7]. This has raised concern as to whether peritoneal dialysis is a good treatment modality in ADPKD patients. Based on clinical experience and evidence from small-scale observational studies [8, 9], however, new opinions have been formed and policy changed. It has recently even been suggested that peritoneal dialysis may be associated with a better prognosis in ADPKD than in non-ADPKD patients [10].

The survival of patients with treated end-stage renal disease for ADPKD was described in the 1990s. These studies showed that ADPKD patients had better survival on RRT than non-ADPKD patients [10–12]. More recent studies have suggested a further improvement in survival, but these studies were performed in relatively small patient populations [13–15]. As a result of this increased survival, the number of ADPKD

patients on RRT and the associated costs for medical care may be expected to have increased. However, there is no recent comprehensive overview of trends in prevalence, incidence, survival and costs associated with RRT for ADPKD.

The European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry and the Euro-CYST consortium have initiated a project to increase knowledge of the epidemiology of RRT for ADPKD in Europe. As part of this project, we investigated the prevalence of RRT and survival after start of RRT (overall and per specific treatment modality) for patients with ADPKD across Europe. Due to the abundance of information data on RRT, incidence will be reported in a separate study.

## MATERIALS AND METHODS

### Data collection

The study population consisted of RRT patients included in the ERA-EDTA Registry, which collects data from 24 national and regional registries in 12 European countries covering a population of 208 million people. Individual patient data, including date of birth, sex, primary renal disease, treatment modality history (haemodialysis, 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). 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 data Table 1.

### Definition

The primary renal disease for which RRT was started was assessed using the ERA-EDTA coding system [16]. Two ERA-EDTA primary renal disease codes can be used for ADPKD: 40 (unspecified polycystic kidney disease) and 41 (polycystic kidney disease adult type). Among countries, a substantial variation (0.1–3.4%) in the mean prevalence of code 40 was observed (see Supplementary data Table 2). We combined codes 40 and 41 for the definition of ADPKD, because the

prevalence of non-ADPKD polycystic kidney disease is expected from clinical experience to be very low, and unlikely to account for figures such as 3.4%.

### Data analysis

The prevalence of RRT and survival after start of RRT (overall and per specific treatment modality) were studied for ADPKD patients and compared with data for non-ADPKD patients (all other RRT patients).

Prevalence was studied in four consecutive 5-year periods (1991–95, 1996–2000, 2001–05 and 2006–10). For each period, we calculated for participating registries the average prevalence of RRT for ADPKD as the sum of the prevalence of ADPKD patients alive and on RRT on 31 December of 5 subsequent years divided by the sum of the total general population covered by that registry in the same 5 years. Treatment modality was defined as the treatment patients were attending at 31 December of each year. The age and sex distribution of the 2005 EU27 population as provided by Eurostat [17] was used to adjust for age and sex, to allow evaluation of trends in time and differences among countries. To investigate the association between prevalence of RRT for ADPKD versus for non-ADPKD, we used weighted least squares regression analysis to take country-specific population sizes into account.

Survival analyses for RRT were performed on incident RRT patients. In addition, survival analyses for dialysis were performed on incident dialysis patients, where treatment modality at Day 91 after the start of RRT was used to categorize subjects into haemodialysis or peritoneal dialysis. For kidney transplant recipients, survival analyses were performed using data after the first transplantation, i.e. such patients could have been on dialysis before transplantation. We used the Kaplan–Meier method and Cox proportional hazards regression to calculate crude and adjusted survival. Data on 2-year survival was used, because 2-year survival was known for all four study periods under investigation. For all survival analyses, death was the event studied and reasons for censoring were loss to follow-up or the end of the follow-up period. Additionally, for survival analyses for dialysis, kidney transplantation was also considered as a censored observation. To allow evaluation of trends over time, and comparisons between ADPKD and non-ADPKD patients, survival analyses were adjusted for age, sex, primary renal disease and country. In addition, survival analyses were performed for patients with primary glomerulonephritis (ERA-EDTA primary renal disease codes 10–19) as an extra control group. Survival analyses were only performed using data from registries that had information over the entire study period (i.e. from 1991 through 2010). Patient survival was calculated not only for the overall RRT population, but also for a specific age group (age 60–65 years at start RRT). For analyses of cause of death, only data from registries reporting <25% missing or unknown causes of death were included. These registries are Austria, Belgium (French-speaking), Denmark, Finland, Greece, Spain (Andalusia, Basque Country, Catalonia and Valencian region), Sweden and the Netherlands. Cause of death was coded using the ERA-EDTA coding system [16]. For analyses of cause of death, RRT modality was determined at 2-year follow-up, or at 60 days prior to death in the case of patients who died before 2-year

follow-up. Regression and survival analyses were carried out using SAS version 9.2.

To determine the economic burden associated with end-stage renal disease for ADPKD, the costs involved with RRT were estimated. Country-specific information obtained from the literature was used. For costs involved with haemodialysis and peritoneal dialysis, data were obtained from: Austria [18], Belgium [19], Denmark [20], Finland [21], France [22], Greece [23], Italy [24], Romania [25], Spain [26], Sweden [27], the Netherlands [28] and the UK [29]. For costs involved with transplantation (first and subsequent years), data were obtained from: Austria [18], Finland [21], France [22], Greece [23], the Netherlands [28] and Spain [26]. Costs were adjusted for currency, and for inflation by harmonized indices of consumer prices as provided by Eurostat. For each RRT treatment modality, the average of the costs obtained from these countries was calculated, together with a 95% confidence interval (95% CI). These numbers were multiplied by the total number of prevalent ADPKD patients per RRT treatment modality in 2010 and summed.

## RESULTS

### Prevalence of RRT

Between 1991 and 2010, a total of 437 496 prevalent patients from 12 countries received RRT; 35 164 patients with ADPKD and 402 332 non-ADPKD patients. Of these patients, 265 866 were male (61%) (18 588 ADPKD patients and 247 278 non-ADPKD patients). Table 1 shows the age- and sex-adjusted prevalence of ADPKD subjects on RRT for the participating countries during four consecutive periods of 5 years. Having observed differences in crude prevalence among European countries, we standardized for the age and sex of the 2005 EU27 population, but differences persisted (Table 1). Prevalence in Denmark, Italy (Calabria), Romania and the UK was below the mean (91.1 per million population [pmp]) whereas, in Belgium, France, Spain and Sweden, the prevalence was above the mean. Figure 1 visualizes these differences geographically. Figure 2 shows per country the prevalence of RRT for ADPKD versus the prevalence of RRT for non-ADPKD in the same time period (2006 through 2010), standardized for age and sex to the 2005 EU27 population. This figure shows a clear positive correlation ( $R^2 = 0.936$ ,  $P < 0.001$ ), indicating that in countries with a high overall number of non-ADPKD patients on RRT, there is also a high number of ADPKD patients on RRT.

### Trends in prevalence of overall RRT

The average prevalence of ADPKD patients receiving RRT increased by 60.4% from 56.8 pmp in 1991–95 to 91.1 pmp in 2005–10 (Table 1). While the prevalence of RRT for ADPKD has increased markedly in Greece and Finland there has been only a modest increase in other countries, such as Denmark and the Netherlands. Figure 3 shows the percentage of prevalent RRT patients with ADPKD for each country and the average for the participating registries with a complete follow-up. The average percentage has remained fairly stable over

Table 1. Prevalence of ADPKD patients receiving renal replacement therapy (RRT) overall (upper panel), and subdivided in dialysis (middle panel) or living with a kidney transplant (lower panel)

	1991–1995 (pmp)	1996–2000 (pmp)	2001–2005 (pmp)	2006–2010 (pmp)	Change <sup>a</sup> (%)
<b>All RRT</b>					
Austria <sup>b</sup>	47.4	60.4	73.0	81.4	+71.7
Belgium <sup>c</sup>	51.4	72.5	88.9	104.1	NA
Denmark <sup>b</sup>	47.4	55.4	64.1	71.1	+50.0
Finland <sup>b</sup>	44.0	62.9	79.1	87.9	+99.8
France				101.5	NA
Greece <sup>b</sup>	38.6	58.1	72.0	78.5	+103.4
Italy, Calabria		64.7	69.5	72.9	NA
Romania				35.9	NA
Spain <sup>c</sup>	80.8	91.5	93.0	103.0	+27.5
Sweden <sup>b</sup>	64.7	77.1	90.4	100.0	+54.6
The Netherlands <sup>b</sup>	56.3	65.0	72.2	80.2	+42.5
United Kingdom <sup>c</sup>	46.4	55.4	61.9	75.6	NA
countries <sup>d</sup>	56.8	70.3	82.1	91.1	+60.4
<b>Dialysis</b>					
Austria <sup>b</sup>	22.4	28.3	30.9	32.3	+44.2
Belgium <sup>c</sup>	33.3	33.1	34.6	37.6	NA
Denmark <sup>b</sup>	22.8	28.9	33.8	33.7	+47.8
Finland <sup>b</sup>	17.9	21.1	23.4	22.5	+25.7
France				39.5	NA
Greece <sup>b</sup>	32.0	48.3	56.0	56.0	+75.0
Italy, Calabria		57.1	57.7	53.4	NA
Romania				34.4	NA
Spain <sup>c</sup>	54.2	47.4	39.9	39.4	NA
Sweden <sup>b</sup>	22.7	26.4	31.1	31.6	+39.2
The Netherlands <sup>b</sup>	28.8	29.3	30.3	26.8	-6.9
United Kingdom <sup>c</sup>	20.7	23.4	26.2	29.9	NA
All countries <sup>d</sup>	32.1	35.8	37.8	37.3	+16.2
<b>Transplantation</b>					
Austria <sup>b</sup>	25.0	32.1	42.1	49.1	+96.4
Belgium <sup>c</sup>	18.1	39.4	54.3	66.3	NA
Denmark <sup>b</sup>	24.6	26.4	30.1	37.0	+50.4
Finland <sup>b</sup>	26.1	41.8	55.7	65.5	+151.0
France				61.6	NA
Greece <sup>b</sup>	6.6	9.8	15.9	22.4	+239.4
Italy, Calabria		7.7	11.8	19.5	NA
Romania				1.4	NA
Spain <sup>c</sup>	26.2	43.5	52.8	63.5	NA
Sweden <sup>b</sup>	42.0	50.7	59.3	68.4	+62.9
The Netherlands <sup>b</sup>	27.5	35.8	41.8	53.4	+94.2
United Kingdom <sup>c</sup>	25.7	29.9	34.3	45.3	NA
countries <sup>d</sup>	24.6	34.4	44.2	53.8	+118.7

All data are standardized to the age and sex distribution of the 2005 EU27 population and expressed per million population (pmp). NA, not applicable or available (due to change in coverage over time).

<sup>a</sup>Change between 1991–1995 and 2006–2010.

<sup>b</sup>Country with complete coverage during all four periods.

<sup>c</sup>Coverage of the general population by the renal registry increasing over time, see for details Supplementary data Table 1.

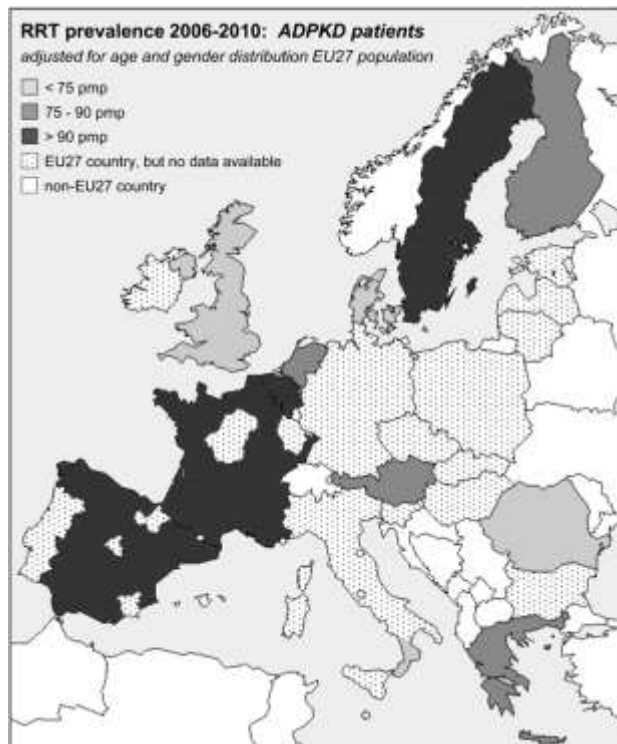
<sup>d</sup>Average of countries with complete coverage during all four periods.

time (9.9% in 1991–95 versus 9.8% in 2006–10), with some exceptions at the country level.

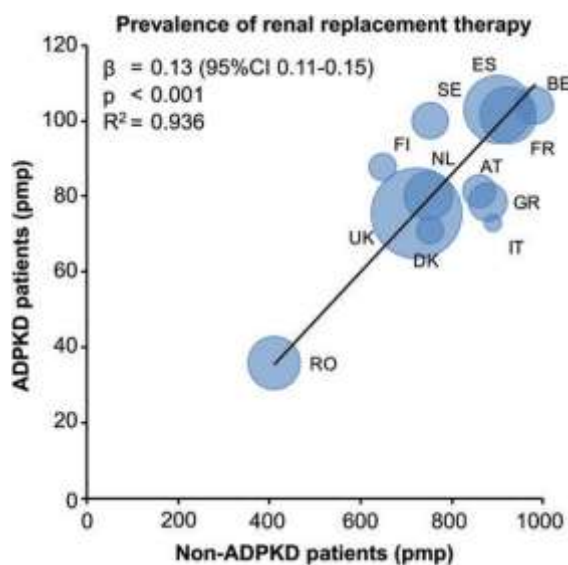
### Trends in prevalence of specific RRT modalities

Over the past 20 years, the prevalence of ADPKD patients treated with the various RRT modalities has changed. The prevalence of haemodialysis increased from 25.2 to 32.0 pmp, peritoneal dialysis increased from 3.8 to 5.3 pmp and kidney transplantation increased from 22.3 to 53.8 pmp (1991–96 versus 2006–10, respectively). In ADPKD patients, the relative contribution to overall RRT decreased for haemodialysis from 49.1 to 35.1%, whereas that of peritoneal

dialysis decreased from 7.4 to 5.8%, and that of kidney transplantation increased from 43.5 to 59.1%. Of note, in non-ADPKD patients, the relative contribution to overall RRT of haemodialysis remained stable at 48.0%, whereas peritoneal dialysis decreased from 9.7 to 7.1% and kidney transplantation increased only slightly from 41.2 to 44.1%. Figure 4 shows the contribution of haemodialysis, peritoneal dialysis and kidney transplantation as a percentage of overall prevalent RRT population in ADPKD versus non-ADPKD patients in the period 2006–10. It indicates that peritoneal dialysis is as frequently applied as a treatment modality in ADPKD as in non-ADPKD patients, whereas ADPKD

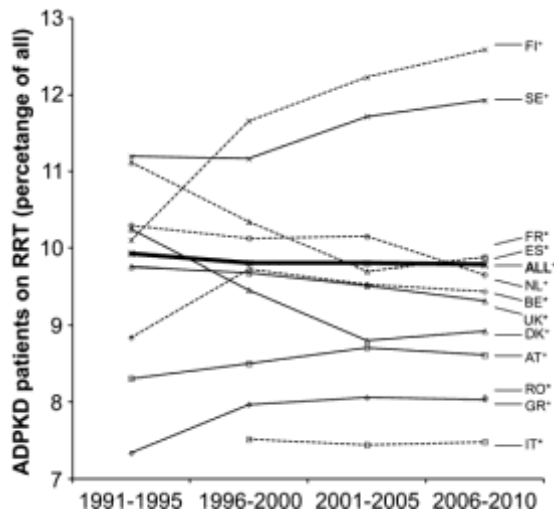


**FIGURE 1 :** Prevalence of renal replacement therapy (RRT) for patients with ADPKD. Data are the average of the period 2006 through 2010, expressed per million population (pmp), and adjusted for age and sex distribution of the 2005 EU27 population.



**FIGURE 2 :** Prevalence of RRT for patients with ADPKD versus non-ADPKD kidney diseases. Data are the average of the period 2006 through 2010, expressed per million population, 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. 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.

patients are more likely to be kidney transplant recipients (especially from a deceased donor rather than a living donor, Supplementary data Figure 1).



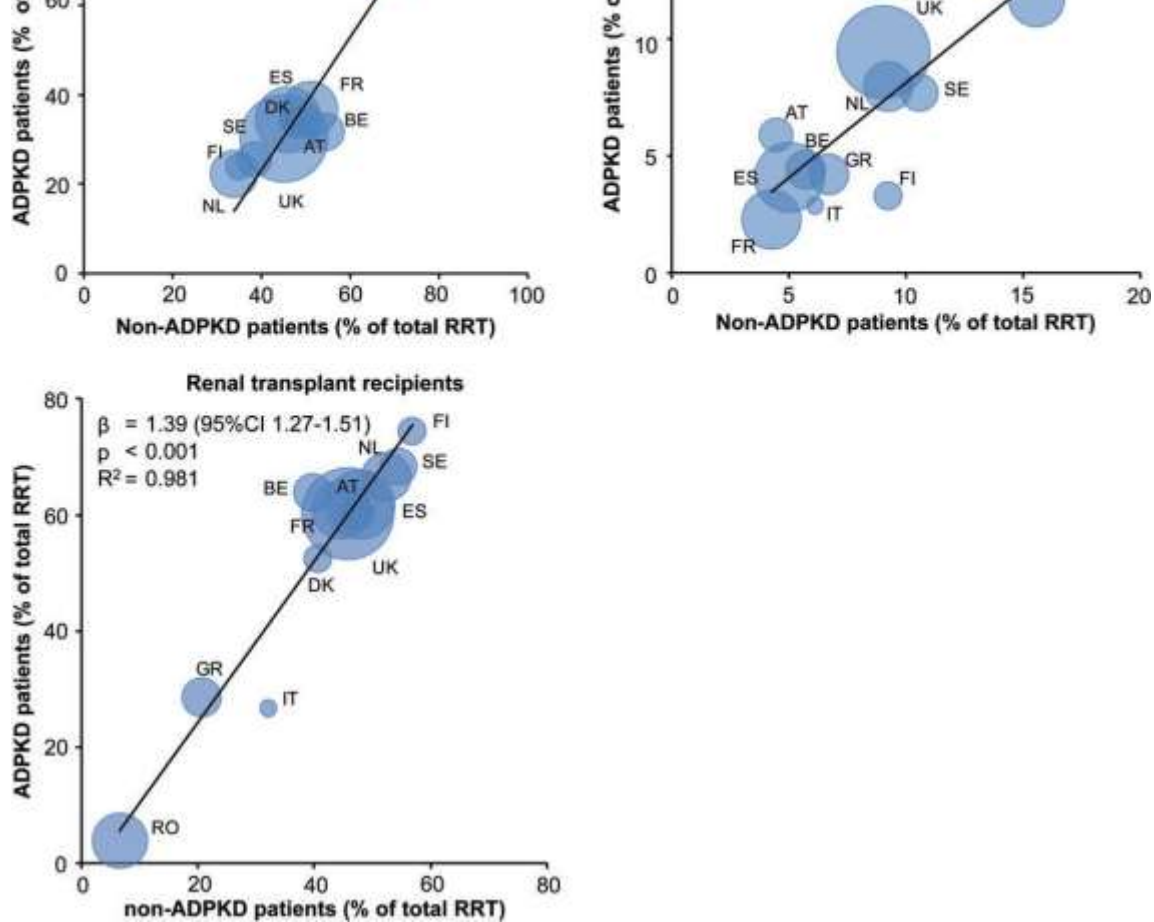
**FIGURE 3 :** Trends in prevalence of ADPKD patients on RRT as percentage of the total population on renal replacement therapy. AT, Austria; BE, Belgium; DK, Denmark; ES, Spain; FI, Finland; FR, France; GR, Greece; IT, Italy, Calabria; NL, the Netherlands; RO, Romania; SE, Sweden; UK, United Kingdom. \*Coverage increasing over time, see for details Supplementary data Table 1. †All countries with complete follow-up coverage.

### Trends in survival

The incidence rate of RRT for ADPKD remained relatively stable at 7.6 versus 8.3 pmp [30]. The crude 2-year survival rate of incident ADPKD patients starting RRT increased from 88.3% in 1991–95 to 90.8% in 2006–10. When using the first time period as reference, this corresponds with a hazard ratio (HR) for total mortality in the later study period of 0.77 (95% CI 0.66–0.90) (Table 2). When adjusted for age, sex and country, the HR for total mortality was even lower at 0.64 (95% CI 0.55–0.75), indicating that 2-year mortality has decreased by 36% in the most recent compared with the first time period (Table 2). When the dialysis modalities are studied separately, it shows that adjusted mortality decreased by 45% in ADPKD patients starting peritoneal dialysis, whereas mortality decreased by only 25% in ADPKD patients starting haemodialysis. The adjusted mortality of kidney transplantation recipients decreased by 48% (Table 2). The adjusted survival on RRT is higher in female than in male ADPKD patients (Supplementary data Table 3), and is higher in ADPKD patients than in non-ADPKD patients (overall, as well as when only patients with primary glomerulonephritis were studied as control group, Supplementary data Table 4). The average age at which dialysis is started, or the transplantation is performed, may differ between ADPKD and non-ADPKD patients. Therefore, we calculated also survival rates for a specific age group (60–65 years) to allow a fair comparison between ADPKD and non-ADPKD. Figure 5 shows that, also in this age group, ADPKD patients starting dialysis, or receiving a kidney transplant, have a higher survival compared with non-ADPKD patients.

### Trends in causes of death

The primary causes of death were divided into five categories (Figure 6). Cardiovascular disease was the most



**FIGURE 4:** Patients on haemodialysis (upper panel), peritoneal dialysis (middle panel) and living with a kidney transplant (lower panel) as percentage of the total population on RRT with ADPKD versus non-ADPKD. 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. 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.

common cause of death in both ADPKD and non-ADPKD patients. During the study period, the relative contribution of cardiovascular mortality to total mortality decreased from 53 to 29% (a decrease of 44%) in ADPKD patients and from 44 to 35% (a decrease of 20%) in non-ADPKD patients. These data indicate that, in 1991–95, the relative contribution of cardiovascular mortality to total mortality was higher in ADPKD patients than in non-ADPKD patients whereas, in 2006–10, the opposite was true. Additional analyses showed that, in ADPKD patients, stroke mortality decreased from 10.0 to 6.7% (a decrease of 33%) in 1990–95 to 2006–10. In a sensitivity analysis using an extended definition for cardiovascular mortality, i.e. adding mortality due to unknown causes to cardiovascular mortality per se, an even more pronounced reduction in cardiovascular mortality was noted in ADPKD

patients when compared with non-ADPKD patients (a decrease of 23 versus 13%, respectively). No difference in cardiovascular mortality was observed between male and female patients (Supplementary data Table 5). Furthermore, we investigated for ADPKD patients the causes of death per treatment modality separately. For kidney transplant recipients, the relative contribution of cardiovascular mortality to total mortality decreased from 64.4 to 7.5%, for haemodialysis from 50.3 to 26.5% and for peritoneal dialysis from 46.3 to 32.6%.

#### Costs involved with RRT

This sub-study includes data from 12 registries (Supplementary data Table 6) and comprises ~42% of the total population of the 27 European Union countries. In this population, the costs involved with RRT for the 20 983 prevalent



Table 2. Two-year patient survival rate and hazard ratio for mortality in ADPKD patients starting RRT, dialysis or receiving a first kidney transplant

All RRT	N	Crude	Adjusted <sup>a</sup>	Crude	Adjusted <sup>b</sup>
1991–1995	2756	88.3 (87.1–89.3)	89.0 (87.8–90.2)	1 (ref)	1 (ref)
1996–2000	3279	88.9 (87.9–89.8)	90.3 (89.3–91.3)	0.94 (0.81–1.10)	0.88 (0.75–1.02)
2001–2005	3547	89.4 (88.5–90.3)	91.6 (90.7–92.5)	0.90 (0.77–1.04)	0.75 (0.65–0.88)
2006–2010	3708	90.8 (89.9–91.7)	92.8 (92.0–93.6)	0.77 (0.66–0.90)	0.64 (0.55–0.75)
<b>Haemodialysis</b>					
1991–1995	1984	89.0 (87.6–90.3)	90.4 (89.0–91.7)	1 (ref)	1 (ref)
1996–2000	2488	88.1 (86.9–89.3)	90.2 (89.0–91.4)	1.10 (0.91–1.33)	1.03 (0.85–1.25)
2001–2005	2573	88.5 (87.3–89.6)	91.5 (90.4–92.6)	1.07 (0.88–1.29)	0.89 (0.73–1.07)
2006–2010	2550	90.2 (89.0–91.3)	92.8 (91.8–93.9)	0.90 (0.74–1.10)	0.75 (0.61–0.91)
<b>Peritoneal dialysis</b>					
1991–1995	606	86.2 (83.2–88.6)	88.0 (84.6–91.5)	1 (ref)	1 (ref)
1996–2000	622	91.9 (89.4–93.8)	92.9 (90.5–95.3)	0.57 (0.39–0.84)	0.58 (0.39–0.86)
2001–2005	748	93.8 (91.7–95.3)	94.6 (92.7–96.5)	0.42 (0.28–0.62)	0.42 (0.28–0.63)
2006–2010	789	91.7 (89.4–93.5)	93.1 (90.9–95.3)	0.57 (0.40–0.82)	0.55 (0.38–0.80)
<b>Transplantation</b>					
1991–1995	815	94.2 (92.5–95.6)	90.6 (87.9–93.4)	1 (ref)	1 (ref)
1996–2000	1505	94.8 (93.6–95.8)	91.9 (90.0–93.8)	0.90 (0.62–1.29)	0.86 (0.60–1.24)
2001–2005	1862	95.3 (94.2–96.1)	93.2 (91.7–94.6)	0.82 (0.57–1.17)	0.72 (0.50–1.03)
2006–2010	2538	96.4 (95.6–97.1)	94.9 (93.8–96.1)	0.60 (0.42–0.86)	0.52 (0.36–0.74)

Hazard ratios are based on 2-year survival.

<sup>a</sup>Adjusted for fixed values of age (at start RRT/dialysis or kidney transplantation), sex and country.

<sup>b</sup>Adjusted for age (at start RRT/dialysis or kidney transplantation), sex and country.

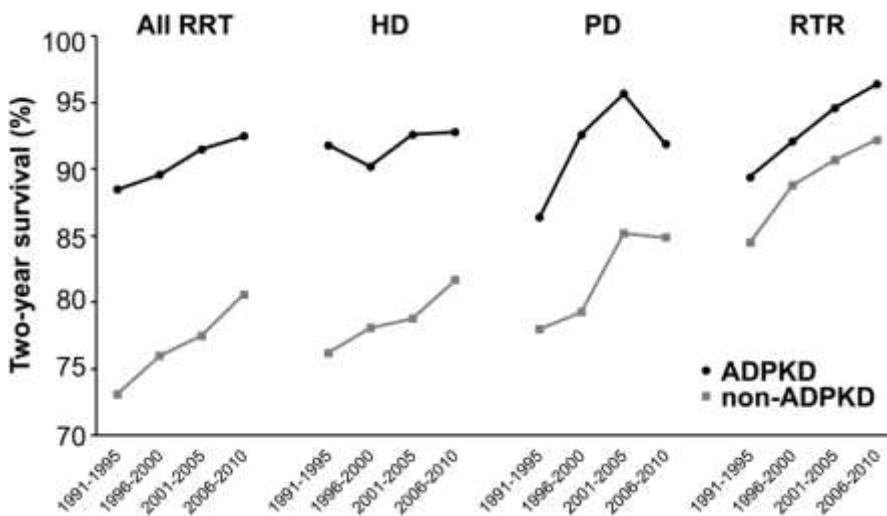


FIGURE 5: Trends in 2-year patient survival in ADPKD versus non-ADPKD patients aged 60–65 years starting RRT, dialysis or receiving a first kidney transplant. Adjusted for age at start RRT, sex and primary renal disease (diabetes, hypertension, glomerulonephritis and other). Survival probabilities are standardized according to the following fixed values: age = 60, males = 60%, diabetes = 20%, hypertension = 17% and glomerulonephritis = 15%. RRT, renal replacement therapy; HD, haemodialysis; PD, peritoneal dialysis; RTR, renal transplant recipients.

ADPKD patients receiving RRT in 2010 (number of patients on haemodialysis 7457, peritoneal dialysis 1078, first year of transplantation 1636 and later after transplantation 10 812) are estimated to be ~651 million euro per year with a 95% CI of 473–829 million euro. Using these data, it can be extrapolated that in the 27 countries that are part of the European Union, ~50 000 ADPKD patients received RRT in 2010, and that the costs involved with RRT for these patients were 1.5 billion euro (95% CI 1.1–2.0 billion euro).

## DISCUSSION

This study shows that across Europe the prevalence of ADPKD patients being dependent on RRT has increased considerably between 1991–95 and 2006–10. It also indicates that the relative contribution of ADPKD to end-stage renal disease for which RRT is started has remained fairly stable during this period (~10%). When compared with non-ADPKD patients

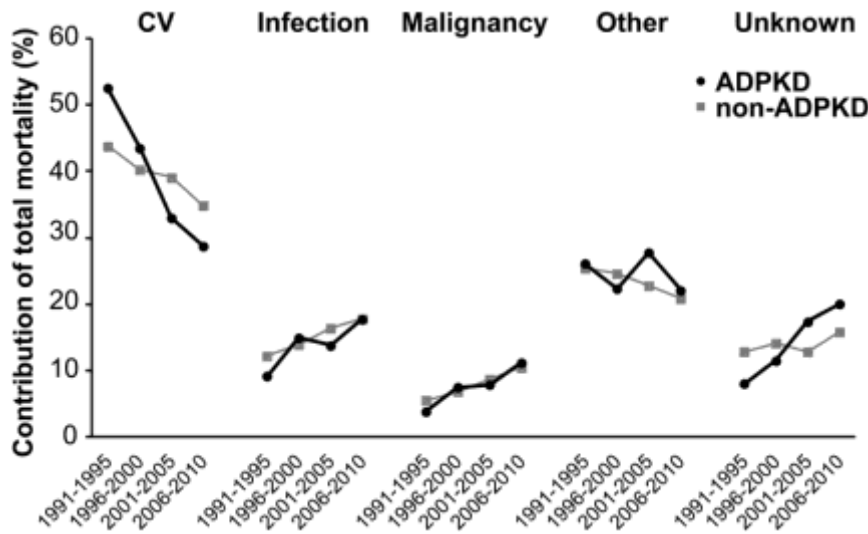


FIGURE 6: Trends in causes of death in patients on renal replacement therapy for ADPKD and non-ADPKD. Adjusted for average age and gender distribution of all patients starting RRT between 1991 and 2010. CV, cardiovascular.

on RRT, ADPKD patients are as likely to be receiving peritoneal dialysis and more likely to be living with a kidney transplant. The survival of ADPKD patients on RRT has improved significantly, mainly due to a marked reduction in cardiovascular mortality.

Differences in the prevalence of RRT for ADPKD were observed among the countries participating in the ERA-EDTA registry. There are at least three possible explanations for these differences. First, a difference in prevalence could be explained by a difference in general population structure among the countries. However, after standardization for age and sex to the 2005 EU27 population differences in prevalence remained. Second, the prevalence of the disease itself may be different between the participating countries. Several studies from Germany, France, Portugal and the United Kingdom have tried to establish country-specific ADPKD prevalence data [31–34]. Unfortunately, different methods were used in these studies making it difficult to draw firm conclusions on this issue. Third, the participating countries may have different policies with respect to acceptance of patients for RRT programmes. Interestingly, we found that the ratio of ADPKD versus non-ADPKD patients on RRT was remarkably stable between countries. Countries with a low overall number of patients receiving RRT have also a low number of ADPKD patients receiving RRT and vice versa. It seems unlikely that countries with a low or high prevalence of ADPKD will have a proportionally low or high prevalence of non-ADPKD chronic kidney disease. These data raise the possibility that differences among countries in prevalence of RRT for ADPKD are a reflection of differences in RRT acceptance policies that are dependent on social and economic motivations [35, 36], but it may also be that prevention or primary care is better in some countries, which affect ADPKD and non-ADPKD to the same extent. However, as yet there is no treatment of which it is known to affect the course of ADPKD.

With respect to the different RRT modalities, we observed that kidney transplantation is a more frequently used modality in ADPKD patients compared with non-ADPKD patients. This is in line with literature [11]. A case–control study from

the USRDS found that ADPKD patients were transplanted at a 2-fold higher rate than controls. This may be due to the fact that, in general, ADPKD patients are younger when they reach end-stage renal disease than non-ADPKD patients [30]. However, even after adjustment for age, it appeared that more ADPKD patients were kidney transplant recipients than non-ADPKD patients, especially of kidneys of deceased donors (Supplementary data Figure 1). It may well be that this is due to ADPKD patients having less co morbidity and therefore they are more likely to be accepted on the transplant waiting list. With respect to peritoneal dialysis, ADPKD patients were as likely to be on this treatment modality as non-ADPKD patients, and mortality in these ADPKD patients after starting peritoneal dialysis was lower. Of course, selection bias should be considered, because patients with very large polycystic kidneys and/or livers may be offered peritoneal dialysis less often [37], but these data suggest that peritoneal dialysis is a safe treatment option in ADPKD patients that reach end-stage renal disease.

We observed a 60.4% increase in the prevalence of ADPKD subjects on RRT from 1991–95 to 2006–10. The prevalence of RRT is influenced predominantly by two factors, incidence of RRT and survival on RRT. We have observed in the countries participating in the ERA-EDTA registry that the incidence rate of RRT for ADPKD remained relatively stable at 7.6 pmp in 1991–95 versus 8.3 pmp in 2006–10 [30]. Because of the abundance of information, data on incident RRT will be presented in detail in a separate report. In contrast, survival on RRT has improved considerably in ADPKD patients, making it the major contributing factor to the increase in the number of ADPKD patients being dependent on RRT. In line with the literature, we have shown that ADPKD patients have a better survival compared with non-ADPKD patients, even after age and sex adjustment [12]. Further, we add to the existing literature that ADPKD patients have better survival than patients with a kidney-localized disease (i.e. patients with primary glomerulonephritis, Supplemental data Table 4). Of note, the choice for a specific RRT modality is not a random process,

but influenced by personal preferences of patients and their treating physicians. In addition, for this analysis, the survival of dialysis patients was determined from the start of RRT, whereas the survival of kidney transplant recipients was determined from the date of their first transplant, and many will have been treated with dialysis before their transplantation. These considerations mean that survival should not be compared between the various RRT treatment modalities, but they do allow evaluations of trends in time per treatment modality and comparisons between ADPKD and non-ADPKD patients per treatment modality.

The increase in survival that we observed is especially due to a marked reduction in cardiovascular mortality, which was more evident in ADPKD patients than in non-ADPKD patients. This reduction in cardiovascular mortality was not caused by a reduction in stroke, but mainly due to a decrease in non-stroke cardiovascular mortality. The cause of this improvement in cardiovascular mortality cannot be concluded from the present study. Observational studies have suggested that better risk factor management before and after start of RRT (i.e. improved blood pressure and cholesterol control) and improvements in quality of coronary interventions (i.e. CABGs and PCIs) may have played a role [38–41], but it could also be due to an improvement in quality of RRT.

The costs involved with RRT for ADPKD for the EU27 zone in 2010 were estimated to be ~1.5 billion euro (95% CI 1.1–1.9 billion euro). To reduce the economic burden for the community at large, and of course to reduce the loss of quantity and quality of life of ADPKD patients, it is of utmost importance to prevent end-stage renal disease in this patient group. For a long time, no treatment options were available to prevent renal function decline in this patient group. Recently, however, it has been shown in a large-scale RCT that the use of the vasopressin V2 receptor antagonist tolvaptan are associated with a decrease in rate of kidney growth and renal function decline when compared with placebo [42]. However, this drug has not yet been registered for the indication ADPKD and is associated with side effects. Other treatment options are therefore necessary. A limited number of these have been tested in clinical trials and, sometimes, the results were promising [43–46]. The efficacy of these novel treatments, however, needs confirmation in large-scale RCTs before they can be prescribed in clinical practice. Given these considerations, more funding for ADPKD-related clinical care and research is urgently needed to allow studies developing and testing new therapies.

We acknowledge that this study has limitations. Firstly, the costs involved with RRT are difficult to determine. Country-specific data on costs associated with RRT were obtained from the literature, but they differ with respect to costs that are taken into account. Some countries included costs of for instance medication, staffing and laboratory analyses, whereas other countries did not. The costs involved with RRT for ADPKD that we calculated should therefore be used as an estimate rather than as an exact figure. It should be noted that the true economic burden is likely to be considerably higher than this figure, because it only relates to medical costs involved with RRT and not costs associated with for instance the loss of

money-earning capacity and the medical complications of the affected patients. Secondly, not all countries in the European Union are participating in the ERA-EDTA Registry and for participating registries detailed information was not complete for all time periods. Average values for the evaluation of trends in time and survival analyses were, therefore, only calculated for countries that did have complete datasets during the four study periods. Notwithstanding, this study still covers 42% of the inhabitants of the European Union, representing more than 200 million people. This study reports, therefore, on by far the most comprehensive epidemiological dataset on ADPKD to date. The study also took into account not only ADPKD, but also non-ADPKD patients on RRT, studied the prevalence of RRT overall and per treatment modality and investigated trends in RRT prevalence and survival over a 20-year time period.

In summary, these data provide the most comprehensive insight thus far into the epidemiology of end-stage renal disease for ADPKD for which RRT has been started. These data show that, in Europe, the prevalence of RRT for ADPKD has markedly increased during the last two decades, but that the relative contribution of ADPKD to the overall RRT population has remained stable at ~10%. Importantly, the survival of ADPKD patients on RRT has increased significantly, mainly due to a reduction in cardiovascular mortality.

## SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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## CONFLICT OF INTEREST STATEMENT

None declared.

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## APPENDIX

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