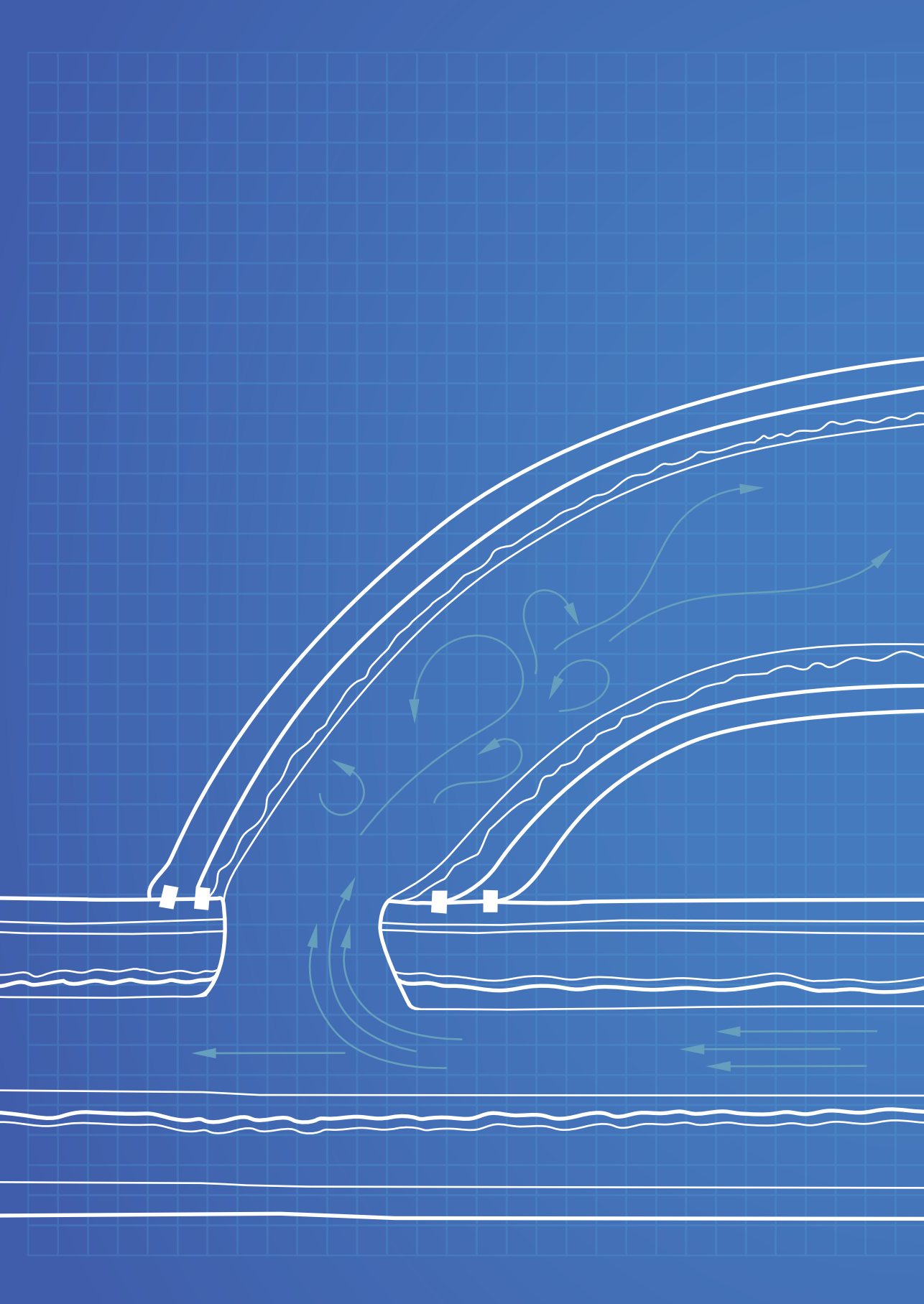
Under construction: improving arteriovenous fistula maturation

Laboyrie, S.L.



Chapter 5

Vascular access outcomes in patients with autosomal dominant polycystic kidney disease

Suzanne L. Laboyrie, Maria K. Svensson, Sabine H. Josemans, Birgitta Sigvant, Joris I. Rotmans, Gunilla Welander

Kidney360. 2024 Jun 1;5(6):877-885

Abstract

Background

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a leading hereditary cause of end-stage kidney disease (ESKD), often utilising hemodialysis as a form of kidney replacement therapy. Patients with ADPKD may also present with extrarenal manifestations, including arterial aneurysms. The gold standard for hemodialysis access is an arteriovenous vascular access (VA), such fistulas (AVFs) or grafts (AVGs). However, limitations, such as low VA flow and inadequate AVF outward remodelling, impact VA utilization. This study aimed to explore whether ADPKD impacts patency rates of AVFs/AVGs in comparison to other underlying ESKD causes.

Methods

We conducted a retrospective cohort study using data from the Swedish Renal Registry from 2011 to 2020, with follow-up until 2022. We included 496 ADPKD patients and 4321 propensity-score matched controls. VA patency rates of ADPKD patients were compared to those of non-ADPKD patients using Kaplan-Meier survival curves and the Mantel-Cox log-rank test. Interventions to maintain or restore patency were also analysed.

Results

Patients with ADPKD constituted 8.0% of all patients, with a higher proportion in the pre-ESKD phase during VA creation (51.6% vs. 40.6%). No significant differences were observed in primary, post-cannulation primary, secondary, or functional patency between ADPKD and non-ADPKD patients. However, more VAs were ligated in ADPKD patients (10.5% vs. 7.7%, p=0.03), and they underwent more first interventions to re-establish flow (49.4% vs. 41.9%, p=0.02).

Conclusions

These findings suggest that AVF/AVG patency remains comparable in ESKD patients with or without ADPKD, and vascular access monitoring and treatment strategies for ADPKD patients should align with those for individuals with other ESKD causes.

Introduction

Patients with end-stage kidney disease (ESKD) require kidney replacement therapy (KRT). Seventy percent of ESKD patients is treated with hemodialysis (HD) [1], for which a well-functioning vascular access (VA) is needed. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommends an arteriovenous fistula (AVF) or graft (AVG) as the preferred type of VA [2]. However, low flow due to stenosis or occlusion is a major complication, limiting the use of AVFs and AVGs for HD. Once the VA can be used for HD, luminal narrowing through intimal hyperplasia and complications such as steal syndrome and aneurysm formation still pose challenges to maintain access patency. These complications require surgical and endovascular interventions and entail a large burden on both the patient and society. Therefore, understanding how individual patient characteristics can affect VA outcomes is of utmost importance.

There are many risk factors influencing VA patency, such as sex, age, co-morbidities and race [3-6]. However, whether the underlying cause of renal failure affects access outcome is often overlooked. Approximately 9% of patients with ESKD have Autosomal Dominant Polycystic Kidney Disease (ADPKD) as their underlying disease [7]. The majority of patients with ADPKD on HD utilize an AVF as vascular access [8]. Patients with ADPKD have an increased incidence of aneurysm formation, mainly intracranial and abdominal [9-12], indicating altered vascular remodelling and an increase in outward remodelling in the vessels, but inducing complications on the long-term. Increased AVF dilatation has also been observed in patients with ADPKD [13], with a higher frequency of AVF aneurysms compared to other patients with ESKD [14]. Lee et al. [15] recently showed that Taiwanese patients with ADPKD have a higher risk of AVF and AVG dysfunction in the period between the first and tenth year after VA creation when compared to other HD patients. They did not report on the impact of this increase in dysfunction, or whether it affected patency of the VAs. To evaluate the prognosis of AVFs/AVGs in European patients with ADPKD, who may have a different genetic background [16], and if ADPKD affects patency rates, we performed a retrospective cohort study using the Swedish Renal Registry, encompassing all patients with kidney disease nationwide.

Materials and Methods

Study design and patient selection

The Swedish National Quality Registry for Renal Failure (SRR) is a web-based registry of patients with treated kidney disease, with national coverage. The dataset is a validated resource for current vascular access care, with high external and internal validity [17]. The present study was approved by the Regional Ethical Review Board in Uppsala (Dnr 2017/047 and Dnr 2022-07164-02).

We included all patients that received an AVF or AVG between 2011-2020, with a follow up of at least two years. Analyses was limited to the first AVF/AVG that was created during our inclusion period. Underage individuals (<18 years) were excluded from our dataset, as well as VAs that were created in the lower limbs or deemed as technical failures. Technical failure was defined as abandonment within 3 days after creation, based on the definition of immediate vascular access failure described by Lee et al. [18]. Patients that received an AVF/AVG but never proceeded to HD treatment due to receiving a donor kidney or not progressing to KRT at all were also excluded from analysis. Secondly, if patients were already on dialysis and never had a first cannulation nor received an intervention we excluded them from our dataset, as this might indicate continued use of a previous VA – such as a central venous catheter - for HD. To avoid confounding by indication, AVFs/AVGs that received an intervention or had a first cannulation but not used for HD were included. This resulted in inclusion of 496 patients with ADPKD, and 5675 patients without ADPKD who received an AVF or AVG. The ADPKD diagnosis in Sweden is made through radiological imaging and the patient's family history. While planning for vascular access surgery, pre-operative investigational mapping is performed using duplex ultrasound, with a general cutoff value of 2 mm in diameter. The individual surgeon however decides whether a patient is eligible or not. This is influenced by the health of the vessels, such as the degree of arterial atherosclerosis and distensibility of the vein.

Definition of endpoints

First cannulation is cannulation of the vascular access with one needle to assess if the VA can be punctured, and a functional start of the AVF/AVG indicates three successive hemodialysis session with two-needle cannulation. Assisted maturation indicates a functional start that was achieved after an intervention. Maturation without an intervention was defined as an intervention-free functional start.

Primary patency was defined as intervention free VA survival, and spans from the date of VA creation until the first intervention, abandonment, end of the observation period or censoring, whichever occurred first. Post-cannulation primary patency was the period from the first cannulation of the VA until the first intervention, abandonment, end of the observation period or censoring. Secondary patency (cumulative survival of the VA) is defined as the time of VA creation until abandonment, end of the observation period or censoring, including all performed interventions. Functional patency spanned from the date of first cannulation until abandonment, end of observation period or censoring, including all performed interventions. Survival curves were plotted until 100 months, due to low number of people at risk in the last months of follow up (100 to 140 months).

Abandonment indicated functional loss of the VA, due to occlusion or ligation, the patient refusing use, or creation of a new VA. Censoring occurred when the patient was lost to follow-up due to emigration or death, or when the patient switched to a different KRT modality such as donor kidney transplantation or peritoneal dialysis.

First interventions performed were categorised as interventions to maintain or re-establish flow. Interventions to maintain flow included percutaneous transluminal angioplasty (PTA), ligation of collateral veins, flow reductional interventions and transpositions for VAs that were not a two-stage brachiobasilic AVF. Interventions to re-establish flow included thrombectomies, anastomosis revisions and thrombolysis.

Statistical analyses

The information that was retrieved from the SRR was compiled from the SRR datasets on chronic kidney disease, vascular access and patent characteristics. This was combined into one dataset matched on the unique vascular access ID number using Python.

Baseline characteristics were summarized as mean ± SD for continuous variables and compared using the t-test, and frequency (percentage) for categorical variables, such as types of primary intervention, were analysed using the chi-square test. The ADPKD group (496 patients) versus non-ADPKD controls (6171 patients) in our dataset had different baseline characteristics (Table 1) and were therefore matched on using propensity score matching based on the covariates sex, age, location of the VA and the phase of kidney failure (having a transplant, being in chronic kidney failure or receiving dialysis). Nearest neighbour matching in a 1:10 ratio was performed using the MatchIt package [19] in R-studio, with a 0.1 calliper.

Histograms of the propensity scores of the two groups before and after matching can be found in supplementary figure 1.

Primary, post-cannulation primary, secondary and functional patency rates were presented as survival analyses using Kaplan–Meier curves and the Mantel-Cox log rank test. IBM SPSS Statistics version 29 was used for all analyses (IBM Corp., Armonk, NY).

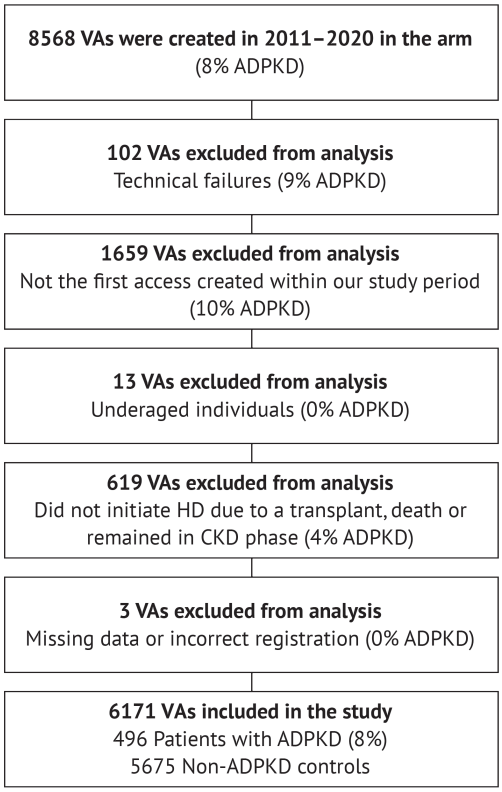


Figure 1: Study flow chart. Overview of the process of establishing the complete dataset of patients receiving an AVF or AVG between 2011-2020. The percentage of individuals with ADPKD in each flow chart box indicate the percentage of the excluded AVFs/AVGs per exclusion criterium that belong to patients with ADPKD. ADPKD = Autosomal dominant polycystic kidney disease, CKD = Chronic kidney disease, HD = hemodialysis, VAs = Vascular access: arteriovenous fistulas and grafts.

Results

Characteristics of patients receiving an arteriovenous access

We retrieved all 8568 AVFs/AVGs from the SRR that were created in the arm between 2011 and 2020. After excluding VAs according to defined exclusion criteria's (Figure 1), 6171 patients were included, of which 8 % with ADPKD (n=496) and 5675 patients with other kidney diseases (non-ADPKD controls). The baseline characteristics of the two groups are shown in Table 1. There were more female patients (44.8% versus 32.3%, p=0.001) and patients pre-emptively receiving an VA (51.6% versus 41.6%) in the ADPKD group, whereas the majority of the control group (non-ADPKD) received dialysis treatment when undergoing VA surgery (38.3% of patients with ADPKD versus 52.5% non-ADPKD). A majority of the VAs in our cohort was created pre-emptively, but only 55 individuals (0.9%) who received an AVG/AVF did not progress to dialysis treatment during the observation period. VA configurations were similar across the two groups, with radiocephalic AVFs as the most common (61% in both groups).

After propensity score matching, the dataset included 496 patients with ADPKD and 4321 matched controls (non-ADPKD). Their baseline characteristics are shown in Table 2.

Table 1: Baseline characteristics of Swedish patients that received an AVF or AVG in the arm between 2011-2020 in Sweden.

Characteristic	Non-ADPKD patients (N=5675)	ADPKD patients (N=496)	P-value
Age, mean years (SD)	63.9 (14.7)	61.2 (12.2)	0.001
Sex, N (%)			0.001
Male	3844 (67.7)	274 (55.2)	
Female	1831 (32.3)	222 (44.8)	
Anticoagulation, N (%)			0.42
Yes	1006 (17.7)	81 (16.3)	
No	1153 (20.3)	113 (22.8)	
Unknown	3516 (62.0)	302 (60.9)	
Cause of renal failure, N (%)			0.001
ADPKD	0 (0.0)	496 (100)	
Glomerulonephritis	896 (15.8)		
Pyelonephritis	191 (3.4)		
Hypertension	1049 (18.5)		
Renovascular disease	31 (0.5)		
Diabetic nephropathy	1643 (29.0)		
Unknown uremia	636 (11.2)		
Other	1229 (21.7)		
Type of VA, N (%)			0.204
Radiocephalic AVF	3485 (61.4)	303 (61.1)	
Brachiocephalic AVF	1209 (21.3)	92 (18.5)	
Brachiobasilic AVF	194 (3.4)	22 (4.4)	
Forearm AVG	61 (1.1)	5 (1.0)	
Upper arm graft	601 (10.6)	56 (11.3)	
Forearm AVF other	125 (2.2)	18 (3.6)	
Phase at VA surgery, N (%)			0.001
Pre-emptive	2305 (40.6)	256 (51.6)	
On dialysis	3004 (52.9)	190 (38.3)	
Kidney transplant	198 (3.5)	35 (7.1)	
Unknown	168 (3.0)	15 (3.0)	
Comorbidities, N (%)			
Haematological malignancy	122 (2.1)	1 (0.2)	0.12
Skin malignancy	47 (0.8)	1 (0.2)	0.31
Other malignancy	502 (8.8)	21 (4.2)	0.002
Diabetes mellitus	2202 (38.8)	30 (6.0)	0.001
Ischemic heart disease	910 (16.0)	31 (6.3)	0.001
Treated for hypertension	3586 (63.2)	306 (61.7)	0.8
Cardiovascular disease	398 (7.0)	32 (6.5)	0.89
Peripheral vascular disease	392 (6.9)	10 (2.0)	0.001

Dialysis includes both peritoneal and hemodialysis. The list of causes of renal failure listed as "other" can be found in supplementary table 1. ADPKD = Autosomal dominant polycystic kidney disease, AVF = arteriovenous fistula, AVG = arteriovenous graft, CKD = chronic kidney disease, VA = Vascular access. Dialysis treatment encompasses both peritoneal dialysis and hemodialysis.

Table 2: Baseline characteristics of patients after performing propensity score matching.

Characteristic	Non-ADPKD patients (N=4321)	ADPKD patients (N=496)	P-value
Age, mean years (SD)	61.8 (14.9)	61.2 (12.2)	0.001
Sex, N (%)			0.11
Male	2549 (59.0)	274 (55.2)	
Female	1772 (41.0)	222 (44.8)	
Anticoagulation, N (%)			0.48
Yes	765 (17.7)	81 (16.3)	
No	887 (20.5)	113 (22.8)	
Unknown	2669 (61.8)	302 (60.9)	
Cause of renal failure, N (%)			0.001
ADPKD	0 (0.0)	496 (100)	
Glomerulonephritis	718 (16.6)		
Pyelonephritis	151 (3.5)		
Hypertension	734 (17.0)		
Renovascular disease	27 (0.6)		
Diabetic nephropathy	1275 (29.5)		
Unknown uremia	470 (10.9)		
Other	946 (21.9)		
Type of VA, N (%)			0.30
Radiocephalic AVF	2566 (59.4)	303 (61.1)	
Brachiocephalic AVF	941 (21.8)	92 (18.5)	
Brachiobasilic AVF	169 (3.9)	22 (4.4)	
Forearm AVG	52 (1.2)	5 (1.0)	
Upper arm graft	494 (11.4)	56 (11.3)	
Forearm AVF other	99 (2.3)	18 (3.6)	
Phase at VA surgery, N (%)			0.001
Pre-emptive	1786 (41.6)	256 (51.6)	
On dialysis	2270 (52.5)	190 (38.3)	
Kidney transplant	166 (3.8)	35 (7.1)	
Unknown	99 (2.3)	15 (3.0)	
Comorbidities, N (%)			
Haematological malignancy	84 (1.9)	1 (0.2)	0.02
Skin malignancy	30 (0.7)	1 (0.2)	0.41
Other malignancy	384 (8.1)	21 (4.2)	0.01
Diabetes mellitus	1684 (39.0)	30 (6.0)	0.001
Ischemic heart disease	648 (15.0)	31 (6.3)	0.001
Treated for hypertension	2729 (63.2)	306 (61.7)	0.78
Cardiovascular disease	285 (6.6)	32 (6.5)	0.96
Peripheral vascular disease	277 (6.4)	10 (2.0)	0.001

Dialysis includes both peritoneal and hemodialysis**.** The list of causes of renal failure listed as "other" can be found in supplementary table 1. ADPKD = Autosomal dominant polycystic kidney disease, AVF = arteriovenous fistula, AVG = arteriovenous graft, CKD = chronic kidney disease, VA = Vascular access. Dialysis treatment encompasses both peritoneal dialysis and hemodialysis.

Functional start of the vascular access

Patients with ADPKD had a similar proportion of absence of a recorded functional start as non-ADPKD patients (20.0% versus 19.6%, p=0.83). Although non-significant, slightly more patients with ADPKD had an intervention free functional start (65.1% vs 62.8%, p=0.13, Table 3). There was no difference in the percentage of patients with assisted maturation (14.9% of patients with ADPKD and 17.6% of patients with non-ADPKD p=0.32). There was a weak correlation between the time from VA surgery to first cannulation / functional use for HD and the duration until loss of primary patency: Pearson correlation efficient 0.20 / 0.17 in our ADPKD patients and 0.16 / 0.15 for non-ADPKD patients (p<0.001 in all analyses).

Subsequently, we analysed the subgroup of patients that were already on dialysis when receiving an AVF/AVG. Patients with ADPKD already on dialysis when receiving a VA had a longer period between surgery and functional start of the VA than controls (non-ADPKD) (122 vs 117 days, p=0.01, Table 3). They also experienced a longer interval between first cannulation and use of the VA (37 vs 28 days p=0.02, Table 3) compared to other patients with ESKD that were on dialysis.

Table 3: Maturation outcomes and time until use of the vascular access.

	Non-ADPKD patients	ADPKD patients	P-value
No functional start, N (%)	845 (19.6%)	99 (20.0%)	0.83
Intervention-free functional start, N (%)	2714 (62.8%)	323 (65.1%)	0.13
Mean time from VA surgery to functional start in days (95% CI)	117 (110 – 124)	122 (102 – 143)	0.01
Mean time from first cannulation to functional start in days (95% CI)	28 (25 – 32)	37 (25 – 49)	0.02

Time until functional start and between first cannulation and functional start was analysed in the subset of patients that already received dialysis when undergoing VA surgery. N = 1797 non-ADPKD patients (79%) and 141 ADPKD patients (90%) that were on dialysis when receiving their VA and had a functional start of the newly created VA. Significance was assessed with the Pearson Chi-Square test. ADPKD = Autosomal dominant polycystic kidney disease, VA = Vascular access: arteriovenous fistulas and grafts

First interventions ending primary patency

Half of all patients underwent one vascular access-related intervention at minimum during follow up (51.8% of patients with ADPKD vs 52.1% in controls, p=0.91, Table 4). Around 3% of all primary interventions was performed to reduce flow (3.1% of primary interventions in ADPKD patients and 2.9% in controls, p=0.71). ADPKD patients had more first interventions to re-establish flow when compared to non-ADPKD controls (49.4% vs 41.9%, p =0.02), while more non-ADPKD patients received interventions to maintain VA patency (53.6% vs 46.7% of

ADPKD patients, p=0.04), other interventions were hybrid or not defined. Overall, patients with ADPKD had fewer interventions per year of functional patency than non-ADPKD controls (1.15 ± 0.13 SEM, vs 1.30 ± 0.05, p <0.001).

Table 4: Patency rates at month 3, 1 year and 3 years

	3 months		1 year		3 years	
Patency	Non-ADPKD	ADPKD	Non-ADPKD	ADPKD	Non-ADPKD	ADPKD
Primary	77.5 %	79.8%	41.2%	45.6%	17.8%	21.4%
Post-cannulation primary	72.1%	75.3%	45.2%	48.0%	20.1%	21.6%
Secondary	90.5%	90.5%	72.7%	75.2%	40.3%	42.9%
Functional	92.8%	94.3%	76.3%	79.0%	40.1%	42.2%

Primary, post-cannulation primary, secondary and functional patency rates at different time intervals: 3 months, 1 year and 3 years, expressed as percentage of all vascular accesses within the analysis subset. ADPKD = Autosomal dominant polycystic kidney disease

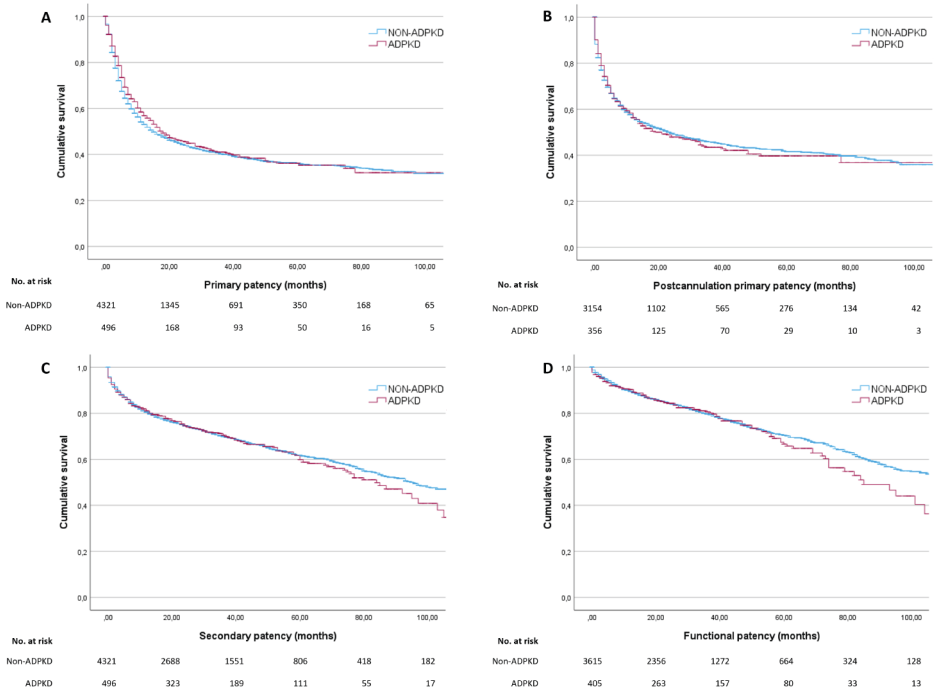


Figure 2: Survival curves of patency outcomes. Primary (A), post-cannulation (B), secondary (C), and functional patency (D) in months for arteriovenous fistulas and grafts in ADPKD patients and controls.

VA patency did not differ between ADPKD and non-ADPKD patients

Median follow up time in ADPKD group was 30 months, and 28 months in the non-ADPKD group ($p < 0.001$). Table 4 shows the patency rates at 3 months, 1 year and 3 years in ADPKD patients and non-ADPKD controls, which were higher in ADPKD patients. Patients with ADPKD did not have different VA outcomes compared to non-ADPKD controls (Figure 2): median primary patency of ADPKD patients was 18 months, versus 15 months in non-ADPKD controls (p=0.33). Post-cannulation primary patency was 21 months versus 24 months (p=0.80) respectively. Long term patency was also comparable: secondary patency was median 84 months in patients with ADPKD and 95 months in non-ADPKD controls (p=0.40), functional patency 85 months versus 112 months (p=0.15).

Table 5: Vascular access interventions and end of use.

	Non-ADPKD	ADPKD	P-value
Received a first intervention, N (%)	2251 (52.1%)	257 (51.8%)	0.91
Primary intervention to maintain patency, N (%)	1206 (53.6%)	120 (46.7%)	0.04
Primary intervention to re-establish patency, N (%)	944 (41.9%)	127 (49.4%)	0.02
VA is abandoned, N (%)	1437 (33.3%)	181 (36.5%)	0.15
Received a transplant kidney, N (%)	489 (11.3%)	96 (19.4%)	0.001
VA is ligated, N (%)	333 (7.7%)	52 (10.5%)	0.03

Ligation can occur due to aneurysm formation of the VA, bleeding of the VA, high flow or steal syndrome. ADPKD = Autosomal dominant polycystic kidney disease, VA = Vascular access: arteriovenous fistulas and grafts

End of use of the vascular access

More patients with ADPKD received a donor kidney (19.4% vs 11.3%, p=0.001, Table 5), and more VA were abandoned, although non-significant (36.5% vs 33.3%, p=0.15). Ligation of the VA, due to complications such as steal syndrome, high flow, bleeding or aneurysm formation of the VA, was more common among patients with ADPKD (10.5% vs 7.7%, p=0.03).

Discussion

In the present study, we hypothesized that ADPKD may affect vascular access patency. However, patency of AVFs and AVGs in patients with ADPKD did not differ compared to patients with other causes of ESKD. We did not observe any significant differences in short-term VA patency. About 20% of all AVFs/AVGs did not have a functional start and this is comparable to outcomes in other cohorts [20-22]. Although not statistically significant, mean primary patency appeared

to be higher in patients with ADPKD, and more patients with ADPKD achieved an intervention-free functional start of the VA. However, after about 5 years, secondary and functional patency rates seemed worse in patients with ADPKD.

A previous study in Taiwan showed that only on the long term (1 to 10 years post VA surgery), incidence rates of AVF/AVG dysfunction were higher in patients with ADPKD [15]. However, they did not elaborate on the functionality or patency rates of AVFs/AVGs in patients with ADPKD. By using the Swedish renal registry, we aimed to create a representative cohort of patients with ADPKD in Europe and add to previous findings from Taiwan by generating more data on the functionality of VAs created in patients with ADPKD. The SRR is a nation-wide quality register in which loss of follow-up only occurs when patients emigrate, and thus enables analysis of large patient groups. Since ADPKD affects the vasculature due to the genetic mechanisms underlying ADPKD, we therefore aimed to evaluate AVF/AVG patency in our cohort of patients with ADPKD and without ADPKD.

Mutations in the PKD1 or PKD2 gene account for about 93% of polycystic kidney disease cases, and the remaining 7% of patients with cystic kidneys have either an undiagnosed mutation, or a mutation in genes that are involved in PKD protein trafficking or biogenesis (GANAB, DNAJB11, IFT140 or ALG9) [23-28]. PKD1 and PKD2 are expressed in endothelial cells and vascular smooth muscle cells and encode Polycystin proteins -1 and -2 [29]. Polycystin-1 and -2 help maintain vessel wall integrity and regulate extracellular matrix homeostasis [30-32]. The Polycystin proteins together form an ion channel complex regulating calcium influx and are involved in sensing mechanotransduction and fluid flow [33, 34]. Thus, it could be hypothesised that vascular remodelling occurs differently in patients with ADPKD compared to other receiving an AVF or AVG, as shown by their tendency to develop intracranial and abdominal aneurysms [9-12] and in AVFs specifically [14]. We did observe increased frequency of VA ligation in patients with ADPKD, however, the reason for ligation was not registered, so we cannot report the numbers on aneurysm development and required interventions. Nonetheless, since ligation is performed after complications such as high flow, aneurysm formation, excessive bleeding of the VA or steal syndrome, this might indicate that patients with ADPKD have altered vascular remodelling that facilitates increase in blood flow more adequately than other underlying reasons for ESKD. In both groups, time until functional was comparable to the reported 3.5 months in a systematic review by Bylsma et al. covering 50 articles reporting time until maturation [35].

A large fraction of vascular accesses in our dataset are created pre-emptively. Since there are national recommendations in place to screen for chronic kidney disease in patients with increased risk – e.g. individuals with diabetes mellitus, hypertension or cardiovascular disease – and equal access to healthcare, CKD patients are referred to the nephrologist early on. More than 80% of the patients on dialysis are already registered in the SRR before initiation of dialysis, and pre-emptive VAs are seen as a quality indicator for adequate patient monitoring and care. It is thought that fistula creation before HD initiation does not affect primary or secondary patency [36]. Moreover, due to the hereditary aspect of the disease, most patients with ADPKD are known and monitored early on by nephrologists. This enables timely access planning or opting for a (pre-emptive) transplant. In our cohort, more patients with ADPKD received their vascular access earlier on, before requiring KRT, and were thus less uremic at the initiation of HD, requiring fewer dialysis sessions or starting at a later time point. This could explain the five-day longer interval from surgery to functional initiation of the vascular access in patients with ADPKD, despite fewer patients requiring an intervention to start using the VA. Patients from the USA using a CVC when receiving an AVF/AVG showed an association between the number of interventions needed to achieve maturation and the risk of losing primary patency [37], however we observed a weak correlation between the time until first cannulation or functional start and the duration until loss of primary patency in our dataset for both ADPKD and non-ADPKD patients receiving an AVF/AVG.

Compared to other patients with non-diabetic ESKD and patients with non-ADPKD diseases on HD, patients with ADPKD have increased survival rates and better overall health [38, 39], which is also reflected by the low prevalence of diabetes mellitus and peripheral vascular disease in our ADPKD cohort. This could counteract some of the ADPKD-related intrinsic vascular changes affecting vascular access maturation. Timely diagnosis and referral to the nephrologist also supports planning for transplantation, so that relatively healthy patients with ADPKD transitioned from HD to transplantation, while sicker patients remained on HD. This may pose a selection bias negatively affecting long term secondary and functional patency analysis.

To minimize loss of power we performed one to many propensity score matching, with a calliper of 0.1. This resulted in fuzzy matching regarding the phase of kidney failure when the patients received their AVF/AVG. The large number of pre-emptive fistulas created in patients with ADPKD compared with controls, where half of the patients already received dialysis, could explain why more patients

with ADPKD underwent first vascular access interventions to re-establish patency. Patients receiving dialysis visit the hospital about three times a week, where the new vascular access is monitored by the dialysis nurse, while a pre-emptive fistula or graft undergoes clinical evaluation about four to six weeks post-surgery, using duplex ultrasound. The delayed monitoring and more sensitive evaluation might result in both prolonged progression of stenosis, quick detection of a potential stenosis, and more severe interventions such as a thrombectomy or anastomosis revision to ensure functionality of the vascular access for future use. Overall, patients with ADPKD did have less interventions per functional patency years than controls. The large number of patients and long follow up in the Swedish Renal Registry allows for subgroup analysis, which can help answer pressing research questions in the field of vascular access, such as whether VAs created in pre-ESKD have differential outcomes and interventions compared to vascular accesses created when the patient already undergoes KRT. Future research should investigate the effect of phase of kidney failure on VA functionality.

The prevalence of patients with ADPKD with an AVF/AVG in our dataset was 8%. This is comparable to the prevalence of patients with ADPKD on KRT in the SRR, which ranged from 10 to 13% over the last decade, similar to the prevalence reported in Europe [7]. Only one third of patients with non-ADPKD receiving an AVF/AVG were female. It is known that although CKD is more prevalent in women, kidney failure progresses more quickly to ESKD in men than women [40]. Biological aspects could underlie the more rapid progression in men, but also personal preferences for KRT modality can explain why more men proceed to HD treatment [40, 41]. The sex discrepancy in progression to ESKD is also present in patients with ADPKD [8, 42-44], although to a much lesser extent when compared to other types of kidney failure.

There were several factors limiting our study. Firstly, not all complications are registered in the SRR as they are registered only when resulting in an intervention. This might result in underrepresentation of overall complications. Secondly, we cannot report the size of the AVF or the vessels that were used for VA surgery since data on pre- and post-operative diameters of the artery, vein and AVF are not reported in the registry. Thirdly, we can only report on the use of anticoagulation (yes/no), but not the exact medication that was given.

In conclusion, no significant differences in AVF/AVG outcomes were observed in patients with ADPKD compared to patients with other underlying causes of ESKD. This suggests that clinical recommendations for differential monitoring and treatment of VA access is not warranted for patients with ADPKD.

Supplementary data

Histograms of the propensity scores per group before and after propensity score matching (supplementary figure 1) and a list of causes of renal failure registered as 'other' in our dataset can be found in the supplementary data.

References

40. Johansen, K.L., et al., *US Renal Data System 2020 Annual Data Report: Epidemiology of Kidney Disease in the United States*. American Journal of Kidney Diseases, 2021. **77**(4, Supplement 1): p. A7-A8.

41. Lok, C.E., et al., *KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update*. American Journal of Kidney Diseases, 2020. **75**(4): p. S1-S164.

42. Ernandez, T., et al., *Risk Factors for Early Failure of Native Arteriovenous Fistulas*. Nephron Clinical Practice, 2005. **101**(1): p. c39-c44.

43. Lok, C.E., et al., *Risk Equation Determining Unsuccessful Cannulation Events and Failure to Maturation in Arteriovenous Fistulas (REDUCE FTM I)*. Journal of the American Society of Nephrology, 2006. **17**(11).

44. Miller, C.D., M.L. Robbin, and M. Allon, *Gender differences in outcomes of arteriovenous fistulas in hemodialysis patients*. Kidney International, 2003. **63**(1): p. 346-352.

45. Woo, K., et al., *Variations in outcomes of hemodialysis vascular access by race/ethnicity in the elderly*. Journal of Vascular Surgery, 2017. **65**(3): p. 783-792.e4.

46. Astley, M.E., et al., *The ERA Registry Annual Report 2020: a summary*. Clinical Kidney Journal, 2023: p. sfad087.

47. Budhram, B., et al., *End-Stage Kidney Disease in Patients With Autosomal Dominant Polycystic Kidney Disease: A 12-Year Study Based on the Canadian Organ Replacement Registry*. Can J Kidney Health Dis, 2018. **5**: p. 2054358118778568.

48. Cagnazzo, F., et al., *Intracranial aneurysms in patients with autosomal dominant polycystic kidney disease: prevalence, risk of rupture, and management. A systematic review*. Acta Neurochirurgica, 2017. **159**(5): p. 811-821.

49. Sung, P.H., et al., *Risk of aortic aneurysm and dissection in patients with autosomal-dominant polycystic kidney disease: a nationwide population-based cohort study*. Oncotarget, 2017. **8**(34): p. 57594-57604.

50. Kato, A., et al., *Abdominal aortic aneurysms in hemodialysis patients with autosomal dominant polycystic kidney disease*. Nephron, 2001. **88**(2): p. 185-6.

51. Irazabal, M.V., et al., *Extended follow-up of unruptured intracranial aneurysms detected by presymptomatic screening in patients with autosomal dominant polycystic kidney disease*. Clin J Am Soc Nephrol, 2011. **6**(6): p. 1274-85.

52. Hadimeri, H., et al., *Dimensions of arteriovenous fistulas in patients with autosomal dominant polycystic kidney disease*. Nephron, 2000. **85**(1): p. 50-3.

53. Jankovic, A., et al., *Arteriovenous Fistula Aneurysm in Patients on Regular Hemodialysis: Prevalence and Risk Factors*. Nephron Clinical Practice, 2013. **124**(1-2): p. 94-98.

54. Lee, T.L., et al., *Prognosis of Vascular Access in Haemodialysis Patients with Autosomal Dominant Polycystic Kidney Disease*. Sci Rep, 2020. **10**(1): p. 1985.

55. Yu, C.C., et al., *PKD2 founder mutation is the most common mutation of polycystic kidney disease in Taiwan*. NPJ Genom Med, 2022. **7**(1): p. 40.

56. Welander, G. and B. Sigvant, *Validating vascular access data in the Swedish Renal Registry SRR*. The Journal of Vascular Access, 2021. **22**(4): p. 629-634.

57. Lee, T., et al., *Standardized definitions for hemodialysis vascular access*. Semin Dial, 2011. **24**(5): p. 515-24.

58. Ho, D., et al., *MatchIt: Nonparametric Preprocessing for Parametric Causal Inference*. Journal of Statistical Software, 2011. **42**(8): p. 1 - 28.

59. Voorzaat, B.M., et al., *Patency Outcomes of Arteriovenous Fistulas and Grafts for Hemodialysis Access: A Trade-Off between Nonmaturation and Long-Term Complications*. Kidney360, 2020. **1**(9).

60. Tordoir, J.H.M., et al., *Surgical and Endovascular Intervention for Dialysis Access Maturation Failure During and After Arteriovenous Fistula Surgery: Review of the Evidence*. European Journal of Vascular and Endovascular Surgery, 2018. **55**(2): p. 240-248.

61. Arhuidese, I.J., et al., *Utilization, patency, and complications associated with vascular access for hemodialysis in the United States*. Journal of Vascular Surgery, 2018. **68**(4): p. 1166-1174.

62. *Polycystic kidney disease: the complete structure of the PKD1 gene and its protein. The International Polycystic Kidney Disease Consortium.* Cell, 1995. **81**(2): p. 289-98.

63. Mochizuki, T., et al., *PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein.* Science, 1996. **272**(5266): p. 1339-42.

64. Senum, S.R., et al., *Monoallelic IFT140 pathogenic variants are an important cause of the autosomal dominant polycystic kidney-spectrum phenotype.* The American Journal of Human Genetics, 2022. **109**(1): p. 136-156.

65. Cornec-Le Gall, E., et al., *Monoallelic Mutations to DNAJB11 Cause Atypical Autosomal-Dominant Polycystic Kidney Disease.* Am J Hum Genet, 2018. **102**(5): p. 832-844.

66. Porath, B., et al., *Mutations in GANAB, Encoding the Glucosidase IIα Subunit, Cause Autosomal-Dominant Polycystic Kidney and Liver Disease.* Am J Hum Genet, 2016. **98**(6): p. 1193-1207.

67. Besse, W., et al., *ALG9 Mutation Carriers Develop Kidney and Liver Cysts.* J Am Soc Nephrol, 2019. **30**(11): p. 2091-2102.

68. Griffin, M.D., et al., *Vascular expression of polycystin.* Journal of the American Society of Nephrology, 1997. **8**(4).

69. Zhang, J., et al., *Polycystin-1 Downregulation Induced Vascular Smooth Muscle Cells Phenotypic Alteration and Extracellular Matrix Remodeling in Thoracic Aortic Dissection.* Frontiers in Physiology, 2020. **11**.

70. Mangos, S., et al., *The ADPKD genes pkd1a/b and pkd2 regulate extracellular matrix formation.* Disease Models & Mechanisms, 2010. **3**(5-6): p. 354-365.

71. Weston, B.S., et al., *The polycystin-1 C-type lectin domain binds carbohydrate in a calcium-dependent manner, and interacts with extracellular matrix proteins in vitro.* Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 2001. **1536**(2): p. 161-176.

72. Hanaoka, K., et al., *Co-assembly of polycystin-1 and -2 produces unique cation-permeable currents.* Nature, 2000. **408**(6815): p. 990-994.

73. Nauli, S.M., et al., *Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells.* Nature Genetics, 2003. **33**(2): p. 129-137.

74. Bylsma, L.C., et al., *Arteriovenous Fistulae for Haemodialysis: A Systematic Review and Meta-analysis of Efficacy and Safety Outcomes.* European Journal of Vascular and Endovascular Surgery, 2017. **54**(4): p. 513-522.

75. Jeong, S., et al., *Patency rates of arteriovenous fistulas created before versus after hemodialysis initiation.* PLOS ONE, 2019. **14**(1): p. e0211296.

76. Lee, T., et al., *Long-Term Outcomes of Arteriovenous Fistulas with Unassisted versus Assisted Maturation: A Retrospective National Hemodialysis Cohort Study.* Journal of the American Society of Nephrology, 2019. **30**(11).

77. Perrone, R.D., R. Ruthazer, and N.C. Terrin, *Survival after end-stage renal disease in autosomal dominant polycystic kidney disease: Contribution of extrarenal complications to mortality.* American Journal of Kidney Diseases, 2001. **38**(4): p. 777-784.

78. Spithoven, E.M., et al., *Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival—an analysis of data from the ERA-EDTA Registry.* Nephrology Dialysis Transplantation, 2014. **29**(suppl_4): p. iv15-iv25.

79. Carrero, J.J., et al., *Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease.* Nature Reviews Nephrology, 2018. **14**(3): p. 151-164.

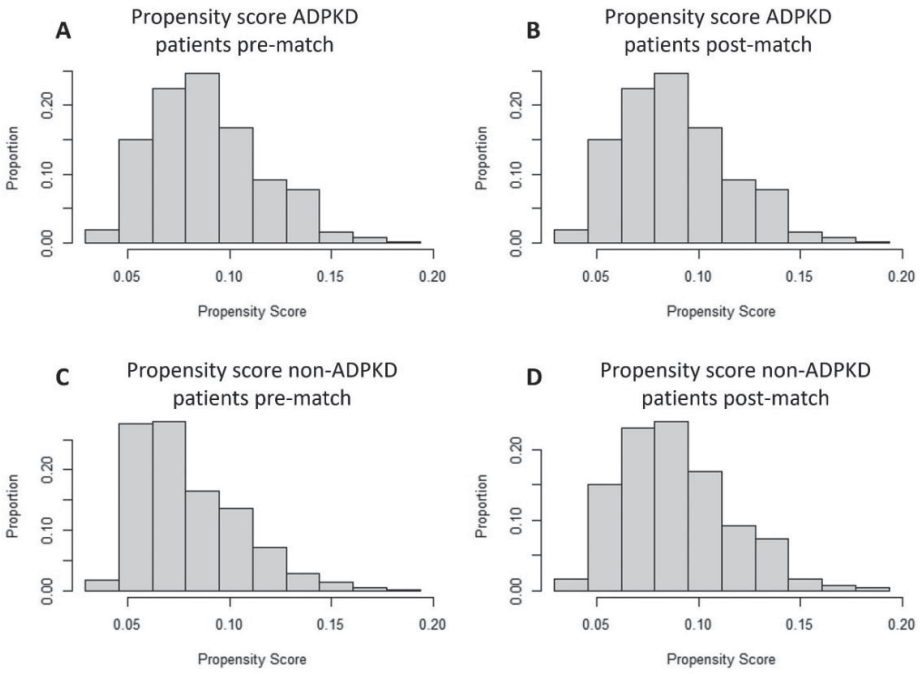
80. Neugarten, J. and L. Golestaneh, *Influence of Sex on the Progression of Chronic Kidney Disease.* Mayo Clinic Proceedings, 2019. **94**(7): p. 1339-1356.

81. Gabow, P.A., et al., *Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease.* Kidney International, 1992. **41**(5): p. 1311-1319.

82. Stewart, J.H., *End-Stage Renal Failure Appears Earlier in Men Than in Women With Polycystic Kidney Disease.* American Journal of Kidney Diseases, 1994. **24**(2): p. 181-183.

83. Schrier, R.W., et al., *Predictors of autosomal dominant polycystic kidney disease progression.* J Am Soc Nephrol, 2014. **25**(11): p. 2399-418.

Supplemental figure and data



Supplementary figure 1: Histogram of the propensity scores before and after matching. Propensity scores of the ADPKD group remained the same before (A) and after (B) propensity score matching: all patients were included in the final dataset. Individuals in the non-ADPKD group had a different distribution before the matching (C), but similar to the ADPKD group after propensity score matching (D).

Supplementary table 1: List of renal diseases classified as 'other' in Table 1 and 2.

EDTA PRD code	ERA-EDTA Primary Renal Diagnosis (PRD) Term
1074	Denys-Drash syndrome
1279	Familial focal segmental glomerulosclerosis (FSGS) - autosomal recessive - no histology
1298	Familial focal segmental glomerulosclerosis (FSGS) - autosomal dominant - no histology
1396	Systemic vasculitis - ANCA positive - no histology
1401	Granulomatosis with polyangiitis - no histology
1417	Granulomatosis with polyangiitis - histologically proven
1429	Microscopic polyangiitis - histologically proven
1438	Churg-Strauss syndrome - no histology
1440	Churg-Strauss syndrome - histologically proven
1455	Polyarteritis nodosa
1464	Anti-Glomerular basement membrane (GBM) disease / Goodpasture's syndrome - no histology
1472	Anti-Glomerular basement membrane (GBM) disease / Goodpasture's syndrome - histologically proven
1486	Systemic lupus erythematosus / nephritis - no histology
1493	Systemic lupus erythematosus / nephritis - histologically proven
1504	Henoch-Schönlein purpura / nephritis - no histology
1515	Henoch-Schönlein purpura / nephritis - histologically proven
1527	Renal scleroderma / systemic sclerosis - no histology
1536	Renal scleroderma / systemic sclerosis - histologically proven
1543	Essential mixed cryoglobulinaemia - no histology
1558	Essential mixed cryoglobulinaemia - histologically proven
1562	Cryoglobulinaemia secondary to hepatitis C - no histology
1570	Cryoglobulinaemia secondary to hepatitis C - histologically proven
1589	Cryoglobulinaemia secondary to systemic disease - no histology
1591	Cryoglobulinaemia secondary to systemic disease - histologically proven
1625	Congenital dysplasia / hypoplasia
1639	Multicystic dysplastic kidneys
1641	Dysplasia due to fetal ACE-inhibitor exposure
1656	Glomerulocystic disease
1660	Congenital pelvi-ureteric junction obstruction
1673	Congenital vesico-ureteric junction obstruction
1687	Posterior urethral valves
1694	Syndrome of agenesis of abdominal muscles - prune belly syndrome
1706	Congenital neurogenic bladder
1710	Bladder exstrophy

EDTA PRD code	ERA-EDTA Primary Renal Diagnosis (PRD) Term
1723	Megacystis-megaureter
1734	Oligomeganephronia
1747	Renal papillary necrosis - cause unknown
1845	Calcium oxalate urolithiasis
1850	Enteric hyperoxaluria
1878	Uric acid urolithiasis
1884	Tubulointerstitial nephritis - no histology
1897	Tubulointerstitial nephritis - histologically proven
1907	Familial interstitial nephropathy - no histology
1911	Familial interstitial nephropathy - histologically proven
1924	Tubulointerstitial nephritis associated with autoimmune disease - no histology
1930	Tubulointerstitial nephritis associated with autoimmune disease - histologically proven
1948	Tubulointerstitial nephritis with uveitis (TINU) - no histology
1953	Tubulointerstitial nephritis with uveitis (TINU) - histologically proven
1969	Renal sarcoidosis - no histology
1976	Renal sarcoidosis - histologically proven
1982	Aristolochic acid nephropathy (Balkan / Chinese herb / endemic nephropathy) - no histology
1995	Aristolochic acid nephropathy (Balkan / Chinese herb / endemic nephropathy) - histologically proven
2005	Drug-induced tubulointerstitial nephritis - no histology
2014	Drug-induced tubulointerstitial nephritis - histologically proven
2022	Nephropathy due to analgesic drugs - no histology
2033	Nephropathy due to analgesic drugs - histologically proven
2046	Nephropathy due to ciclosporin - no histology
2051	Nephropathy due to ciclosporin - histologically proven
2067	Nephropathy due to tacrolimus - no histology
2079	Nephropathy due to tacrolimus - histologically proven
2080	Nephropathy due to aminoglycosides - no histology
2098	Nephropathy due to aminoglycosides - histologically proven
2108	Nephropathy due to amphotericin - no histology
2112	Nephropathy due to amphotericin - histologically proven
2120	Nephropathy due to cisplatin - no histology
2131	Nephropathy due to cisplatin - histologically proven
2149	Nephropathy due to lithium - no histology
2154	Nephropathy due to lithium - histologically proven
2165	Lead induced nephropathy - no histology

EDTA PRD code	ERA-EDTA Primary Renal Diagnosis (PRD) Term
2177	Lead induced nephropathy - histologically proven
2183	Acute urate nephropathy - no histology
2196	Acute urate nephropathy - histologically proven
2203	Chronic urate nephropathy - histologically proven
2219	Radiation nephritis
2226	Renal / perinephric abscess
2235	Renal tuberculosis
2242	Leptospirosis
2257	Hantavirus nephropathy
2261	Xanthogranulomatous pyelonephritis
2274	Nephropathy related to HIV - no histology
2288	Nephropathy related to HIV - histologically proven
2290	Schistosomiasis
2300	Other specific infection
2407	Ischaemic nephropathy - no histology
2411	Ischaemic nephropathy / microvascular disease - histologically proven
2430	Atheroembolic renal disease - no histology
2448	Atheroembolic renal disease - histologically proven
2476	Renal vein thrombosis
2482	Cardiorenal syndrome
2495	Hepatorenal syndrome
2509	Renal amyloidosis
2513	AA amyloid secondary to chronic inflammation
2521	AL amyloid secondary to plasma cell dyscrasia
2532	Familial amyloid secondary to protein mutations - no histology
2545	Familial amyloid secondary to protein mutations - histologically proven
2550	Familial AA amyloid secondary to familial Mediterranean fever / TRAPS (Hibernian fever) - no histology
2566	Familial AA amyloid secondary to familial Mediterranean fever / TRAPS (Hibernian fever) - histologically proven
2578	Myeloma kidney - no histology
2584	Myeloma cast nephropathy - histologically proven
2597	Light chain deposition disease
2606	Immunotactoid / fibrillary nephropathy
2610	Haemolytic uraemic syndrome (HUS) - diarrhoea associated
2623	Atypical haemolytic uraemic syndrome (HUS) - diarrhoea negative
2634	Thrombotic thrombocytopenic purpura (TTP)
2647	Haemolytic uraemic syndrome (HUS) secondary to systemic disease

EDTA PRD code	ERA-EDTA Primary Renal Diagnosis (PRD) Term
2652	Congenital haemolytic uraemic syndrome (HUS)
2668	Familial haemolytic uraemic syndrome (HUS)
2675	Familial thrombotic thrombocytopenic purpura (TTP)
2681	Nephropathy due to pre-eclampsia / eclampsia
2699	Sickle cell nephropathy - no histology
2702	Sickle cell nephropathy - histologically proven
2741	Autosomal recessive (AR) polycystic kidney disease
2756	Alport syndrome - no histology
2760	Alport syndrome - histologically proven
2773	Benign familial haematuria
2787	Thin basement membrane disease
2794	Cystic kidney disease
2804	Medullary cystic kidney disease type I
2815	Medullary cystic kidney disease type II
2827	Uromodulin-associated nephropathy (familial juvenile hyperuricaemic nephropathy)
2836	Nephronophthisis
2843	Nephronophthisis - type 1 (juvenile type)
2858	Nephronophthisis - type 2 (infantile type)
2862	Nephronophthisis - type 3 (adolescent type)
2870	Nephronophthisis - type 4 (juvenile type)
2889	Nephronophthisis - type 5
2891	Nephronophthisis - type 6
2901	Primary Fanconi syndrome
2917	Tubular disorder as part of inherited metabolic diseases
2929	Dent disease
2938	Lowe syndrome (oculocerebrorenal syndrome)
2940	Inherited aminoaciduria
2955	Cystinuria
2964	Cystinosis
2972	Inherited renal glycosuria
2986	Hypophosphataemic rickets X-linked (XL)
2993	Hypophosphataemic rickets autosomal recessive (AR)
3000	Primary renal tubular acidosis (RTA)
3016	Proximal renal tubular acidosis (RTA) - type II
3028	Distal renal tubular acidosis (RTA) - type I
3037	Distal renal tubular acidosis with sensorineural deafness - gene mutations
3044	Nephrogenic diabetes insipidus

EDTA PRD code	ERA-EDTA Primary Renal Diagnosis (PRD) Term
3059	Lesch Nyhan syndrome - hypoxanthine guanine phosphoribosyl transferase deficiency
3063	Phosphoribosyl pyrophosphate synthetase (PRPPS) superactivity
3071	Alagille syndrome
3085	Bartter syndrome
3092	Gitelman syndrome
3102	Liddle syndrome
3118	Apparent mineralocorticoid excess
3125	Glucocorticoid suppressible hyperaldosteronism
3139	Inherited / genetic diabetes mellitus type II
3141	Pseudohypoaldosteronism type 1
3156	Pseudohypoaldosteronism type 2 (Gordon syndrome)
3160	Familial hypocalciuric hypercalcaemia
3173	Familial hypercalciuric hypocalcaemia
3187	Familial hypomagnesaemia
3194	Primary hyperoxaluria
3207	Primary hyperoxaluria type I
3211	Primary hyperoxaluria type II
3224	Fabry disease - no histology
3230	Fabry disease - histologically proven
3248	Xanthinuria
3253	Nail-patella syndrome
3269	Rubinstein-Taybi syndrome
3276	Tuberous sclerosis
3282	Von Hippel-Lindau disease
3295	Medullary sponge kidneys
3305	Horse-shoe kidney
3314	Frasier syndrome
3322	Branchio-oto-renal syndrome
3333	Williams syndrome
3346	Townes-Brocks syndrome
3351	Lawrence-Moon-Biedl / Bardet-Biedl syndrome
3367	Mitochondrial cytopathy
3379	Familial nephropathy
3380	Acute kidney injury
3398	Acute kidney injury due to hypovolaemia
3403	Acute kidney injury due to circulatory failure
3419	Acute kidney injury due to sepsis

EDTA PRD code	ERA-EDTA Primary Renal Diagnosis (PRD) Term
3426	Acute kidney injury due to rhabdomyolysis
3435	Acute kidney injury due to nephrotoxicity
3442	Acute cortical necrosis
3461	Kidney tumour
3474	Renal cell carcinoma - histologically proven
3488	Transitional cell carcinoma - histologically proven
3490	Wilms tumour - histologically proven
3501	Mesoblastic nephroma - histologically proven
3517	Single kidney identified in adulthood
3529	Chronic kidney disease (CKD) / chronic renal failure (CRF) caused by tumour nephrectomy
3538	Chronic kidney disease (CKD) / chronic renal failure (CRF) due to traumatic loss of kidney
3731	Primary hyperoxaluria type III