

ARegPKD-Newsletter 2016



1. What is the status of the registry?

By September 2016 93 centers from 23 mostly European countries have registered for the study, and >350 patients have been included. The majority of patients are currently followed in pediatric nephrology divisions, yet a substantial number has also been recruited by pediatric gastroenterologists or nephrologists from Internal Medicine. The largest cohorts have been enrolled at centers in Germany, Poland, Turkey and the United Kingdom. Data from more than 1400 visits of more than 300 patients were collected with a follow-up of up to 28 visits. To the best of our knowledge ARegPKD thus represents the largest multinational cohort of ARPKD patients with available detailed clinical data. Currently the first detailed data analyses are underway with a focus on the renal phenotype.

2. What are other important PKD news?

A new gene associated with ADPKD

(Porath B et al. Mutations in *GANAB*, Encoding the Glucosidase IIa Subunit, Cause Autosomal-Dominant Polycystic Kidney and Liver Disease. *The American Journal of Human Genetics*, 2016; 98:1193-1207)

ADPKD is known to be caused by mutations in the genes *PKD1* and *PKD2* encoding the proteins polycystin 1 and polycystin 2, and is accompanied by polycystic liver disease. Autosomal dominant polycystic liver disease (ADPLD) with absent or very few renal cysts is a separate disorder caused by *PRKCSH*, *SEC63* or *LRP5* mutations. Via whole-exome sequencing of genetically unsolved ADPKD and ADPLD families, Porath et al. recently identified mutations in *GANAB* encoding glucosidase II subunit a as new cause for ADPKD and ADPLD. Functional data suggest that glucosidase II is required for correct maturation and localization of the polycystin proteins.

Blood Pressure in Autosomal Dominant Polycystic Kidney Disease

(Schrier RW et al. Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease. *The New England Journal of Medicine*, 2014; 371: 2255-66. Torres VE et al. Angiotensin Blockade in Late Autosomal Dominant Polycystic Kidney Disease, *The New England Journal of Medicine*, 2014; 371:2267-76)

The results of the HALT-PKD trial studying the effect of blood pressure control on ADPKD were published in two manuscripts in *The New England Journal of Medicine*.

In the study by Schrier et al. hypertensive patients in early ADPKD (aged 15 to 49 years with an estimated GFR >60 ml/min/1.73m²) were randomly assigned to either a standard blood-pressure target or a low blood-pressure target (120-130/70-80 mmHg vs. 95-110/60-75 mmHg) and to either an ACE Inhibitor (lisinopril) plus ARB (telmisartan) or lisinopril plus placebo. Rigorous blood-pressure control was associated with a slower increase in total kidney volume as a surrogate marker for disease progression. Yet there was no change in overall estimated GFR, but a greater decline in left-ventricular-mass index and in urinary albumin excretion. The combination of ACEI and ARB did not significantly alter the rate of increase in total kidney volume compared to ACEI alone.

Similar results were shown in the manuscript of Torres et al. studying more progressed ADPKD patients (aged 18-64 years with an estimated GFR of 25-60 ml/min/1.73m²) who received either ACE inhibitor (lisinopril) and placebo or lisinopril and ARB (telmisartan) with doses adjusted to achieve blood pressures of 110-130/70-80 mmHg. There was no significant difference between the study groups with regard to blood pressure control, decline in eGFR and urinary albumin excretion. Interestingly, there was no significant difference in adverse events (hyperkalemia, acute kidney injury).

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Imaging Classification of Autosomal Dominant Polycystic Kidney Disease

(Irazabal MV et al. Imaging Classification of Autosomal Dominant Polycystic Kidney Disease: A Simple Model for Selecting Patients for Clinical Trials. *Journal of the American Society of Nephrology* 2015; 26:160-172)

Phenotype and progression to end-stage renal disease vary grossly among ADPKD patients. In order to select patients who are appropriate for clinical trials or likely benefit from a therapeutic option, the group classified ADPKD patients according to height-adjusted total kidney volume measured with computed tomography/magnetic resonance imaging and three or more eGFR measurements over ≥ 6 months in typical (Class 1) and atypical (Class 2) ADPKD. Atypical ADPKD encompassed unilateral, segmental, asymmetric or uni/bilateral kidney atrophy. Patients of typical (Class 1) ADPKD were further divided into class 1A to 1E, whereby classification and age at measurement of height-adjusted total kidney volume predicted the change in eGFR over time. This classification may e.g. be helpful for patient selection within the frame of clinical trials.

The PROPKD Score: A New Algorithm to Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease

(Cornec-Le Gall E et al. The PROPKD Score: A New Algorithm to Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease. *Journal of the American Society of Nephrology* 2016; 27:942-951)

ADPKD shows significant phenotypic variability with some patients reaching ESRD before the age of 40 years and other never requiring renal replacement therapy. Cornec-Le Gall et al. developed a prognostic model to predict renal outcomes in ADPKD patients on the basis of genetic and clinical data via cross-sectional studying of 1341 patients. A scoring system was developed with factors male sex, hypertension before 35 years of age, first urologic event before 35 years of age and genotype (truncating and non-truncating *PKD1* and *PKD2* mutations) defining three risk categories with low, intermediate and high risk of progression to ESRD with corresponding median ages for ESRD onset of 70.6, 56.9 and 49 years. A score >6 predicts ESRD onset before 60 years of age with a positive predictive value of 90.9%. The score predicts renal outcomes in a heterogeneous cohort thereby enabling personalization of therapeutic management of ADPKD patients.

Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease

(Gansevoort RT et al. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. *Nephrology Dialysis Transplantation* 2016; 31:337-348)

The vasopressin V2 receptor antagonist tolvaptan was approved for use in adult patients with autosomal dominant polycystic kidney disease (ADPKD) and chronic kidney disease stages 1-3 with evidence of rapidly progressing disease. The position statement of the ERA-EDTA Working Groups of Inherited Kidney Disorders and European Renal Best Practice gives a hierarchical decision algorithm allowing risk-factor assessments in a descending order of reliability. Included factors encompass CKD stage by age, eGFR decline, kidney growth, predicted progression by baseline height-adjusted total kidney volume indexed for age and/or genotype including the PRO-PKD score and predicted progression by family history. Thereby patients most benefitting from tolvaptan are aimed to be selected in order to improve benefit-to-risk ratio and cost-effectiveness of the treatment with tolvaptan.