Autosomal dominant polycystic kidney disease
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Thesis summary, discussion and future perspectives
THESIS SUMMARY AND DISCUSSION

Most Autosomal Dominant Polycystic Kidney Disease (ADPKD) patients show progressive kidney function decline and develop end-stage renal disease (ESRD) between their 4th to 7th decade of life.\textsuperscript{1-3} In these patients, progressive cyst formation leads to massive kidney enlargement in both kidneys. Although the genetic basis and the pathophysiology of the disease are nowadays well known, optimal treatment of affected patients remains a major clinical challenge.

This thesis consists of three parts. In the first part, we showed a comprehensive overview of the incidence rate and prevalence of renal replacement therapy for ADPKD, thus defining the scope of the ADPKD associated burden from an epidemiological perspective. In the second part, we investigated various methodological aspects of clinical trial design, with a focus on ADPKD specific issues. We tried to improve feasibility of clinical trials by simplifying the measurement of parameters indicative for disease severity. In the third part, we combined novel methodology and new insight in the pathophysiology of ADPKD to design a large scale randomized clinical trial that investigates the efficacy of a potential renoprotective treatment.

PART 1 EPIDEMIOLOGY OF ADPKD

Two studies are widely cited that estimated the prevalence of ADPKD in the general population.\textsuperscript{3,4} These studies suggest that the prevalence of ADPKD is about 1 per 1000 subjects. Not all of these patients reach end-stage renal disease. Approximately one third of the patients will never need renal replacement therapy. Notwithstanding, ADPKD is one of the most common causes of end-stage renal disease. It is therefore remarkable that the epidemiology of end-stage renal disease due to ADPKD has rarely been studied. This is the more relevant, as such information can help to address the question whether treatment has become available that can postpone the need for renal replacement therapy.

In nephrology in general several treatment options are used to preserve kidney function, i.e. low protein diets, strict blood pressure control and renin-angiotensin-aldosterone system inhibition. These interventions have also been studied in ADPKD patients. The results of these studies were generally interpreted as disappointing. It should be stated though, that the design of these studies was often not optimal due to insufficient power and inclusion of patients relatively early in the disease. In such
patients, renal function remains fairly stable for a long period of time and it is therefore
difficult to prove efficacy of treatments that aim to delay disease progression. A
conclusive answer to the question whether conventional renoprotective treatments
are effective in ADPKD patients is therefore still lacking.

In **Part 1** of this thesis, we investigated the epidemiology of end-stage renal disease
caused by ADPKD for which renal replacement therapy (RRT) was started. For
this purpose we used Registry data of the European Renal Association - European
Dialysis and Transplantation Association (ERA-EDTA). This Registry provided us the
largest epidemiological dataset on ADPKD yet, covering approximately 42% of the
population of the European Union. We studied the population in four consecutive

In **Chapter 2**, we hypothesized that with a stable prevalence of ADPKD in the
general population, change in incidence rates of RRT may provide indications
whether successful renoprotective treatments have emerged for ADPKD during the
last two decades. In the dataset of the ERA-EDTA, we observed a small increase in
average age at onset of RRT from 56.6 years in 1991-1995 to 58.0 years in 2006-
2010, but also an increase in the incidence rate of RRT for ADPKD. We investigated
not only the overall incidence, but also the incidence rate per million of the age
related population. The key finding is that the incidence rate of RRT for ADPKD
remained stable in the age groups up to 50 years during all four consecutive 5-year
periods. We interpreted this that conventional chronic kidney disease treatments
did not decrease the rate of renal function loss and consequently did not postpone
the need for RRT in younger ADPKD patients. In the age groups over 70 years of
age, we observed an increase in incidence rate of RRT for ADPKD. This reflects
probably that nowadays more elderly are accepted to start RRT, because of
change in referral and acceptance policy, or that elderly patients nowadays survive
longer to reach end-stage renal disease due to a decrease in the competing risk
of mortality.

ADPKD patients are in general healthy patients when compared with other patients
on RRT. In **Chapter 3**, we showed that indeed survival on RRT was better for ADPKD
patients than for non-ADPKD patients. Moreover, survival improved considerably
in ADPKD as well as non-ADPKD patients on RRT during the last decades. The
improved survival 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. coronary arterial bypass grafts and percutaneous coronary interventions) may play a role,\textsuperscript{5-8} but it could also be due to for instance an improvement in quality of RRT.

Given the major improvement in survival on RRT, and the slight increase in incidence rate of RRT, the number of ADPKD patients being dependent on RRT has increased considerably the last two decades. The number of patients receiving RRT for ADPKD has increased by 60% in two decades from 57 to more than 90 patients per million population. When we extrapolate this figure to the overall population of the European Union (EU), it can be calculated that in the EU 52,800 ADPKD patients receive some form of RRT in 2013. The costs involved are estimated at €1.5 billion euro per year. These costs are likely to increase further due to the expected further improvement in survival and considering that currently no treatment is available to prevent renal function decline.

Kidney transplantation is the treatment of choice for most patients from a medical point of view as well as from an economic point of view. We showed that the percentage of patients with ADPKD that receives pre-emptive kidney transplantation is already higher than in non-ADPKD patients, but we feel this figure could and should still be increased.

In Chapters 2 and 3 we have defined the scope of the ADPKD related burden from an epidemiological perspective. Our data suggest that conventional chronic kidney disease treatments appear not to have halted disease progression in ADPKD patients. Importantly, these results do not imply that these treatments, i.e. strict blood pressure control, renin-angiotensin-aldosterone inhibition, statins, low-salt and low-protein diets should not be prescribed in ADPKD patients. Although these treatments may not affect renal survival, they are likely to have helped to reduce cardiovascular morbidity and mortality in these patients. Because of the absence of effective treatments to halt disease progression and the improved survival during RRT, the number of patients receiving RRT has increased dramatically and these numbers are expected to rise further. In order to improve the economic burden for the community at large and the loss of quantity and quality of life of these patients, it is of utmost importance to develop new treatments to halt disease progression in ADPKD.
PART 2: METHODOLOGY DEVELOPMENT FOR CLINICAL TRIALS IN ADPKD

When performing randomized controlled trials, it is important to be able to assess adequately disease severity and progression. In most kidney diseases, kidney function is measured for this purpose. Glomerular filtration rate (GFR) is estimated using equations that include besides age and gender, serum creatinine or cystatin C. Creatinine is freely filtered by the glomerulus, but also actively secreted by the proximal tubules in small amounts. Cystatin C is produced in all nucleated cells, also freely filtered by the glomerulus, whereafter it is completely reabsorbed by proximal tubular epithelial cells and degraded. Measurement of GFR with an exogenous marker such as $^{125}$I-iothalamate is considered to be the gold standard, but expensive and inconvenient for patients.

In ADPKD, cysts are formed through epithelial cell proliferation in renal tubules. It has been suggested that in the early stages of ADPKD, cysts mainly develop in the proximal tubules and that cysts from collecting duct cells occur at later stages of the disease. Proximal tubular cells actively secrete creatinine and in healthy individuals this accounts for 10-15% of the total renal creatinine clearance. In ADPKD patients it is likely that proliferation and dedifferentiation of proximal tubular cells results in aberrant tubular secretion of creatinine. In Chapter 4, we showed that ADPKD patients indeed have higher tubular secretion of creatinine than healthy control subjects, but only at high-normal GFR. This increased tubular secretion of creatinine accounts for only 8% of the total creatinine clearance. At lower GFR, no difference in tubular secretion of creatinine was observed between ADPKD patients and healthy controls. This limited change in tubular secretion of creatinine when compared to controls appears to have no major negative effect on the performance of the GFR estimation equations. In Chapter 4, we also showed that change in mGFR correlated well with change in eGFR during 3 years of follow-up. These findings are in line with recent literature. The Consortium for Renal Imaging Studies in Polycystic kidney disease (CRISP) showed that change in mGFR correlated significantly, albeit weaker than with change in eGFR$_{\text{MDRD}}$ after 3 years of follow-up ($r=0.30, p<0.001$). An Italian study, however, suggested that GFR estimation equations were unreliable to estimate GFR and failed to detect changes over time. Differences between our results and this latter study may be explained by different gold-standard GFR measurement techniques, methods to measure creatinine, patient characteristics and duration of follow-up. Plasma iothexol and $^{51}$Cr-EDTA disappearance curves after a single-injection may be less accurate than continuous infusion of $^{125}$I-iothalamate to measure...
GFR. Duration of follow-up in our study was 3 years, whereas it was 1 year in the Italian study. Studies with a prolonged follow-up show in general more change in GFR. Consequently, their results will be less influenced by random measurement variation and true associations will become apparent. Our findings have led us to the conclusion that, for clinical trials as well as clinical care, GFR estimating equations can be used as a substitute for the more time-consuming and invasive gold standard GFR measurement techniques to assess kidney function. For estimation of GFR, correct measurement of plasma creatinine and cystatin C is mandatory. In epidemiological studies and randomized controlled trials, these analytes are often measured in one central laboratory to prevent inter-laboratory variability. In addition, it is recommended to separate plasma or serum from cells shortly after collection. This is done to prevent metabolism and active or passive transport of analytes between the intra- and extracellular compartments. However, when blood samples are collected at a large number of sites, sending whole blood samples to a central laboratory may be more convenient than separating and pipetting these blood samples at individual sites for shipment of plasma. As yet little is known about the effect of delayed separation of whole blood at room temperature on the stability of creatinine. In order to improve feasibility of estimating kidney function, we investigated the effect of delayed separation of whole blood at room temperature on the stability of creatinine and cystatin C. In Chapter 5, we showed that creatinine and cystatin C remain stable in whole blood stored at room temperature for 48 hours before separation. The changes of both analytes during delayed separation period did not induce more variability in measured concentrations and did not affect estimated GFR.

When implementing the findings from Chapters 4 and 5, blood of patients with ADPKD participating in a randomized clinical trial may be withdrawn at their local laboratory and be sent as whole blood sample to the central laboratory. The whole blood samples should arrive there within 48 hours after withdrawal and the correct values of plasma creatinine and cystatin C can be measured. The obtained creatinine and cystatin C values can then be used to estimate GFR. As a result, patients do not have to travel to a central laboratory to have their blood drawn or local laboratories do not have to handle samples prior to shipment to that central laboratory for analyte measurement. This method simplifies blood collection for the patient, the study team and makes it less vulnerable for errors. Of note, plasma samples should be stored at -80°C Celsius and creatinine and cystatin C should preferably be measured after completion of the study with all samples of a single patient in one run to minimise inter-assay variation, and consequently, to obtain the most reliable data with respect to change in kidney function over time.
In ADPKD patients, GFR may not be the best measure to assess disease severity. GFR remains within the normal limits for an extended period before entering a late period of decline towards renal failure.\textsuperscript{17} This phenomenon is assumed to be caused by hyperfiltration of remnant nephrons.\textsuperscript{18} The CRISP consortium showed that kidney enlargement results from the continuous formation and expansion of cysts. Their data suggest that total kidney volume may be a better parameter to assess disease severity, especially in the earlier stages of the disease.\textsuperscript{19} Figure 1 shows total kidney volume in relation to GFR over time. As kidney volume gradually increases, compensatory hyperfiltration by glomeruli maintains GFR within the normal range, despite loss of functional renal parenchyma. When these compensating nephrons also fail, GFR starts to decline. Several studies showed that the rate of increase in total kidney volume can be measured reliably. CT or MR Images are used to measure TKV by summing the products of the area corresponding to the kidney and the slice thickness. The measurement of TKV, however, is difficult and laborious by this method. In case kidney volume can be estimated (eTKV) with high accuracy, precision and reliability, it would alleviate the time-consuming kidney volume measuring process. Recently, two novel kidney volume estimation methods have been proposed.\textsuperscript{20,21} However, these methods have not been externally validated yet.

\textbf{Figure 1.} Schematic representation of GFR in relation to total kidney volume. GFR remains within normal limits for an extended period of time, thereafter declining towards end-stage renal disease (blue). GFR becomes higher than expected from the number of functioning nephrons (red) due to compensatory hyperfiltration of residual functioning glomeruli, whereas total kidney volume (green) increases steadily over time. Figure adapted from Grantham et al.\textsuperscript{22}
In Chapter 6, we validated therefore these kidney volume estimation methods. To investigate reproducibility of the estimations methods, the intra- and inter-coefficient of variations (CV) were determined. Intra- and inter-observer CV of eTKV were low, but higher than the intra- and inter-CV of measured TKV (mTKV). Both TKV estimating methods showed low bias, high precision and moderate accuracy. Although performance for estimated TKV is not perfect, using estimated TKV instead of measured TKV does not lead to significant misclassification for disease prognosis. To assess prognosis, a classification system is used that categorizes patients into 5 classes based on thresholds for height corrected TKV (HtTKV) at a given age (A through E, with A indicating the best and E the worst prognosis with respect to future kidney function decline). Only a limited percentage of patients was reclassified (7-9%), especially to a lower risk classification. In a subgroup, we showed that percentage change in TKV measured by gold-standard method correlates relatively well with percentage change in TKV using both estimation methods. Our findings indicate that TKV estimation methods perform relatively well cross-sectionally, and can therefore be used in clinical care for patients with ADPKD to assess their prognosis. It should be noted that our results with respect to follow-up data are based on a limited number of patients and a larger study is warranted to investigate the performance of estimation methods longitudinally. When these estimation methods are also validated in such longitudinal analyses, these estimating methods may also be used in randomized controlled trials to assess TKV making these trials more feasible.

A third proposed marker to assess disease severity in ADPKD is renal blood flow. The CRISP consortium measured in 131 ADPKD patients renal blood flow by magnetic resonance imaging. They showed that a reduction of renal blood flow paralleled growth of total kidney volume and preceded kidney function decline. However, this has been investigated in a single study, that only included patients with an eGFR >70 ml/min and contrast-enhanced MR images were used. This limits the applicability in patients with impaired kidney function due to the risk of contrast-induced nephropathy and nephrogenic systemic fibrosis. The aim of our study was therefore to investigate whether renal blood flow can be measured accurately by non-contrast MRI in ADPKD patients with relatively preserved as well as impaired kidney function. In Chapter 7, we showed that renal blood flow without using contrast could be measured accurately and reliably in ADPKD patients. However, there are a number of issues rendering such measurement less feasible in ADPKD patients with impaired kidney function. First, in a model used to validate RBF MRI,
we were not able to measure $RBF_{\text{MRI}}$ in the smallest phantom artery, which is a surrogate for more severe ADPKD. Second, intra-observer coefficients of variation were higher in patients with low eGFR than patients with high eGFR. Third, MR images obtained without using contrast resulted less often in interpretable results in patients with lower eGFR; MRI images were judged technically unsatisfactory in 34% of patients with an eGFR $\leq 70$ ml/min$^1$1.73m$^2$ vs. in 16% of patients with an eGFR $>70$ ml/min$^1$1.73m$^2$. Notwithstanding, assessment of renal blood flow may still be of help to measure disease severity and for risk classification, because the clinical need for risk classification in this patient group is especially present early in the disease. At that stage eGFR remains within the normal limits for an extended period of time. At later stage disease, when kidney function starts to decline, eGFR in association to age can be used as parameter to assess disease severity and prognosis.

In 2012, the TEMPO study showed that tolvaptan, a vasopressin V2 receptor antagonist, slowed the rate of growth in total kidney volume and the rate of renal function decline over a period of 3 years in ADPKD patients. Treatment with tolvaptan is therefore promising, but there are also limitations to the use of drug. First, theoretically it will be only effective on cysts expressing the vasopressin-2 receptor. However, cysts may also be formed in nephron segments that do not express this receptor. Second, many ADPKD patients also suffer from liver cysts. Since these liver cysts do not express the vasopressin-2 receptor, tolvaptan will not reduce growth of these cysts. Third, in a PKD1-deletion mouse model, a vasopressin-2 receptor-antagonist was proven effective to reduce cysts growth early in the disease, but it was less effective at later stages of the disease. Since the TEMPO study included only patients relatively early in their disease, no firm conclusions can be drawn whether this drug will also be efficacious in later stage disease. Fourth, treatment with tolvaptan gives undesirable side effects, e.g. thirst, polydypisia, polyuria, nocturia and disturbed night rest, leading to drug discontinuation in a certain percentage of treated patients. Lastly, unexpected liver function test abnormalities were observed in a small number of patients treated with tolvaptan. Especially because of fear for potential hepatotoxicity the United States Food and Drug Administration did not approve tolvaptan as standard care for ADPKD patients yet, and asked for additional information.
PART 3 SOMATOSTATIN THERAPY TO HALT PROGRESSION IN ADPKD

In 2013, promising results were obtained with a somatostatin-analogue with respect to the treatment of ADPKD. The ALADIN Study showed that treatment with Octreotide, a long-acting somatostatin-analogue, causes significantly less increase in total kidney volume when compared to placebo after 1 year, although after 3 years the difference was attenuated and not significant anymore.27 Renal function decline was not significantly different between the two groups over 3 years. This may be due to limited power, because this study included only a small number of patients. However, when the change in GFR is studied from 1 to 3 years after start of treatment, GFR decline was significantly slower in the active treatment group than in the placebo group. This difference is probably explained by the acute hemodynamic effect of the somatostatin-analogue, that causes a reversible, hemodynamic decrease in GFR.28 The study design of the ALADIN Study did not take this acute hemodynamic effect into account. These results are very hopeful and supportive for larger RCT’s with somatostatin analogues, to determine their efficacy to reduce renal function decline and growth in total kidney volume.

In Chapter 8, we describe the rationale and design of such a clinical trial, the DIPAK 1 Study (Developing Interventions to halt Progression of ADPKD). We have implemented the new insights in clinical trial design from Part 2 into the development of a large clinical trial that will investigate the efficacy of the somatostatin-analogue Lanreotide on rate of renal function decline in ADPKD. This multi-center, open-label, randomized, controlled, parallel-arm trial includes ADPKD patients with a high likelihood of disease progression defined as patients with an eGFR between 30-60 mL/min*1.73m², who are aged 18 and 60 years. Sample size calculation suggested that enrollment of 150 of such patients per study group would be necessary. With four centers participating, each center committed itself to enroll 75 patients. The primary endpoint is the rate of change in kidney function in patients treated with Lanreotide on top of standard-care versus patients treated with standard-care only. Rate of change in kidney function is defined as the slope through serial eGFR values over time starting at week 12 of treatment until the end of the treatment phase of the study, hence taking the acute hemodynamic effects of somatostatin-analogues into account. The secondary endpoints of the study are change in kidney volume, liver volume and quality of life. The study started to enroll in June 2012. In August 2014, almost all study participants were enrolled.
FUTURE PERSPECTIVES

Now in 2014, we are on the brink of a new era with respect to the treatment of ADPKD patients. Finally drugs are emerging for this once untreatable disease. However, when we take a closer look at the clinical studies that have been performed thus far, we observe not only positive results, but also side effects of the drugs that have been investigated.

At our center, many patients are treated with the V2R-receptor antagonist tolvaptan. Nearly all these patients suffer from drug-induced polydipsia, polyuria, nocturia and need to drink more than 4 to 5 liters of water daily. These side effects influence daily activities and may have a negative influence on their quality of life. Patients using somatostatin-analogues, i.e. Octreotide or Lanreotide, also suffer from side effects. Abdominal cramps within 12 hours of the injection, diarrhea, and flatulence are common. When after a few injections a steady state with respect to plasma levels of the drug is obtained, the side effects of these somatostatin-analogues partly resolve. Dosage reduction might be an option to decrease the intensity of these side effects. However, this may also result in less renoprotective efficacy of the drug. In this respect low-dose combination therapy could be an interesting option that reduces side effects of the individual drugs, while maintaining full renoprotective efficacy. V2R-antagonists and somatostatin-analogues act via different receptors, but both reduce intracellular production of cAMP in renal collecting duct cells, whereas mTOR-inhibitors act via a different pathway. Figure 2 shows the site of action of these different drugs. All drugs eventually aim to reduce, cell proliferation and consequently cyst formation.

Recently, a combination therapy study was performed in polycystic liver disease. The mTOR-inhibitor everolimus and the somatostatin analogue octreotide were combined to evaluate the efficacy of add-on treatment in 44 patients with symptomatic polycystic liver disease (including 15 ADPKD patients also suffering from polycystic liver disease) in a 48-week follow-up clinical trial. This trial showed no additional effect of everolimus to octreotide for reduction of liver volume in polycystic liver disease. In a secondary analysis including only ADPKD patients, total kidney volume did not change under any treatment regimen. Of note, sample size was not calculated for detecting differences in total kidney volume. This study showed that combination therapy with a mTOR-inhibitor and a somatostatin-analogue was disappointing for polycystic liver disease.
A combination of V₂R-receptor antagonists and somatostatin-analogues might be of more interest for ADPKD patients. V₂R-receptor antagonists have already been proven effective and the prospect for somatostatin-analogues is promising. This combination of drugs might act synergistically to reduce cAMP levels in tubular cells. Combination therapy is interesting for several other reasons. First, combination therapy may improve treatment efficacy, because they may synergistically reduce cAMP in the collecting duct cells. Second, both drugs could be given in an alternating treatment regimen to prevent reduced treatment efficacy due to potential downregulation of the somatostatin or upregulation of the vasopressin-V2 receptor. Third, combination therapy may allow using reduced dosages of these drugs, leading to less side effects, whereas treatment efficacy may still be maintained.

Recently, investigators showed in a PKD¹PC/RC animal model that combination therapy of a V₂R-antagonist and a somatostatin-analogue had a clear additive effect with respect to reduction of cyst growth compared to the separate treatments.³¹ These results are promising and it would be interesting to perform a large scale randomized controlled trial to investigate whether combination therapy indeed enhances the renoprotective effects of both individual drugs via synergistic inhibition of intracellular production of cAMP. The first-arm could include standard-care, the second arm...
treatment with lanreotide and the third-arm combination therapy of lanreotide with tolvaptan. Of note, tolvaptan is not registered for treatment of ADPKD in Europe yet, but the European Medicines Agency will decide on the registration at the end of 2014 and tolvaptan may include standard care if registered in Europe. In the third arm, we should ideally determine the dosage for both drugs based on the dose response curves with respect to the renoprotective as well as the side effects of the drugs. Three split-dose regimen of lanreotide are used: low (60mg s.c. every 28 days), medium (90mg s.c. every 28 days), high (120mg s.c. every 28 days). Subjects begin treatment with the lowest dose, lanreotide 60mg. After safety assessment, and when tolerated, treatment is titrated to the next higher dose. For tolvaptan, three split-dose regimens are used: low (45/15mg daily), medium (60/30mg daily) and high (60/30mg daily), based on earlier studies.25,32

Subjects start with lowest dose and after 1-week safety assessment and when tolerated, treatment is titrated to the next higher dose. This study should have at least 3 years of follow-up and should be powered adequately. The primary endpoint should be a 30% reduction of rate in kidney function loss between standard care and combination therapy. The secondary endpoint should be the number and intensity of side effects between lanreotide-treated and combination therapy treated patients. The patients included should be young and at risk for rapid disease progression. For that purpose the recently proposed risk classifications may be used (see further).

In addition to the development of V2 receptor antagonists and somatostatin analogues, the search for alternative treatments for ADPKD should continue. In 2014, a clinical trial performed in children and young adults showed that the HMG-CoA reductase inhibitor, pravastatin, was effective to slow progression of growth in TKV.33 However, no significant change in creatinine clearance was noted over time, nor between treatment groups. The working mechanism has not been elucidated yet and this study should be considered as a hypothesis generating study, especially because another study in the adult ADPKD population showed no benefit of pravastatin on eGFR decline.34 This latter study, however, may have been underpowered with only 49 patients included and was performed in a (too) early stage of the disease. Further research is therefore needed to investigate the potential renoprotective effect of HMG-CoA reductase inhibitors in a larger randomized clinical trial.

In this new era for treatment of ADPKD patients two new questions come forward; whom should we treat and when should we start treatment in these patients. As we know, the clinical course of ADPKD is highly variable 35 with some patients reaching
end-stage renal disease at a young age, while others never reach this phase during their lifetime. It is important to select only those patients who may benefit from treatment i.e. those patients that are expected to have progressive disease. Recently, two models were developed to select patients for clinical trials and treatment.⁰²,³⁶ One model used besides age and height, estimated TKV while the other model used the genotype of the patient and two clinical variables. The former model divided patients into three different groups characterized by low risk, intermediate risk, and high risk for rapidly progressive disease. The patients in the low risk group should not be selected for treatment to halt disease progression. For those patients, the benefits of the treatment will not outweigh the disadvantages of treatment side effects. For the patients with intermediate risk, their risk should be determined at a yearly basis. The patients in the third group, with a high risk for rapidly progressive disease, are likely to benefit from treatment and are well suited for participation in clinical trials and for treatment in a clinical setting when renoprotective treatments become available. The second model is named the PRO-PKD score and predicts the probability of end-stage renal disease at the age of 60 years.³⁶ This model gives points for hypertension onset before age of 35 years, first urological complication before age of 35 years, and genetic mutation (truncating versus non-truncating PKD1 mutations, and PKD2 mutation). The probabilities ranged from 9.3% (0 points) to 100% (4 points) to have end-stage renal disease at the age of 60 years. This simple PRO-PKD score may be of interest to select patients for clinical trials. Of note, the score did not incorporate kidney function into the score. Urinary biomarkers have also shown to have prognostic value. In our own ADPKD cohort, albuminuria, IgG, KIM-1 and MCP-1 were significantly associated with renal function decline.³⁷ Although, these urinary biomarkers are not routinely determined in the clinical situation (except albumin), and no thresholds were determined for these biomarkers to define which patients are at low, intermediate or high risk for rapidly progressive renal function decline, these biomarkers may become important in the near future to determine the clinical course in ADPKD patients. The next question is when we should start medical treatment of patients at high risk for disease progression, i.e. early or later in the disease? Since ADPKD is a genetic and progressive disease, it would be legitimate to start the treatment early in life to postpone or prevent end-stage renal failure. Somatostatin-analogue and V₂R-antagonists inhibit cyst growth and these drugs do not stop cyst growth nor restore the destroyed renal parenchyma. In addition, V₂R-antagonists are less effective in later stages of the disease.²⁶ Thus, in my view there is no doubt that early treatment would be quintessential.
As discussed above, selection of patients for treatment is of utmost importance. The two aforementioned studies suggest that patients should be selected for treatment based on information obtained from most advanced technology; i.e. genotyping of the patient and measuring TKV by a MRI-scan. To date, we live in the digital era with rapid technological development, also in medicine. However, as a medical doctor it remains important to interact and communicate with your patient. Since ADPKD is an autosomal dominant disease with 100% penetrance, we may also be able to predict the clinical course of ADPKD on the basis of family history, at what age did relatives start renal replacement therapy. The history of these family members may help predict the risk for disease progression in the individual patient. This way of predicting risk for rapid disease progression may well be as adequate as the one obtained by costly most advanced technology. We are currently investigating this hypothesis.

In conclusion, ADPKD may become a treatable disease in the near future. When this is achieved, we should select only those patients at risk for rapid disease progression. This may be done in the future by performing one of the oldest skills of a medical doctor: taking a careful family and medical history.
REFERENCES


