Global Action. Local Change.

KDIGO Controversies Conference on Autosomal Dominant Polycystic Kidney Disease (ADPKD)

January 16-19, 2014
Edinburgh, United Kingdom

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants to determine what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and other times they highlight areas for which additional research is needed to produce evidence that might lead to guidelines in the future.

Background

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most frequent genetic diseases, affecting an estimated 12.5 million people worldwide.[1] The disease is characterized by progressive kidney enlargement caused by the development of multiple cysts in both kidneys. It is associated with the development of hypertension and kidney pain, episodes of cyst hemorrhage, gross hematuria, nephrolithiasis, and cyst infections, and reduced quality of life.[1-4] Renal function is often preserved up to the age of 40, but subsequently the glomerular filtration rate (GFR) decreases and end-stage

renal disease (ESRD) ensues in 50% of patients by the fifth decade.[5] ADPKD is a systemic disease that also affects organs other than the kidney, with potentially serious complications such as massive hepatomegaly and intracranial aneurysm rupture. There is a significant intra-familial and inter-familial variability in the rate of renal disease progression and the spectrum of extrarenal manifestations.

Many important aspects including: 1) the prevalence of *PKD1* or *PKD2* mutations in distinct populations; 2) contribution of genetic and environmental factors to the progression of the renal disease; 3) the occurrence and nature of renal and extrarenal complications; 4) optimal evaluation and treatment of the renal and extrarenal complications; 5) quality of life issues; and 6) health care resource use and the global burden of disease have been studied only in small cohorts. The striking inter- and intra-familial heterogeneity in renal disease progression remains largely unexplained. Recent interventional trials aiming to halt kidney growth and decline of renal function have yielded either disappointing results or moderate delays in rates of disease progression.

ADPKD represents a major burden for public health, estimated at €2 billion of annual health care costs in the EU alone.[6] Research on ADPKD could therefore offer a tremendous return on investment. NIH Director Dr. Francis Collins called PKD, one of the “hottest, most promising areas of research". The *PKD1* and *PKD2* genes that cause ADPKD have been discovered in 1994[7-9] and 1996[10], respectively. Many research groups have made significant contributions regarding the clinical and basic scientific aspects of the disease and, more recently, in the development of therapeutic modalities for ADPKD. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) has shown that height adjusted kidney volume predicts the risk of developing renal insufficiency, thus qualifying it as a prognostic biomarker.[2,11] Kidney volume is

being used as the primary or secondary outcome measure in clinical trials of mTOR inhibitors,[12-13] vasopressin V2 receptor antagonists,[14] somatostatin analogs,[15-18] and renin-angiotensin blockade,[19] but it is not currently accepted by regulatory agencies as an adequate primary endpoint. The identification of surrogate markers to predict the effect of interventions on the course of disease also remains an important goal.[20-23] Specific funding for ADPKD research is highly variable worldwide, reflecting variable awareness from the health authorities and importance of patient organizations.
The patient-oriented research on ADPKD is at a critical stage. The use of modern, cutting-edge diagnostic and genetic technologies in combination with up-to-date imaging techniques, bioinformatics and biostatistics has the potential to identify progression factors and biomarkers, assess disease stage specific mortality, morbidity and health costs, and to improve classification of the patients. However the use of this new knowledge remains highly fragmented and heterogeneous across various regions. As such there is a risk for slow translation into improving diagnostic and therapeutic modalities for patients with ADPKD.

Relevance of the topic and the conference

ADPKD is one of the most frequent genetic diseases and is responsible for up to 10% of ESRD patients. Despite its importance, approaches to the diagnosis, evaluation, prevention and treatment of the renal and extrarenal manifestations of ADPKD vary widely and no widely accepted practice guidelines exist for this disease.

Research groups have made significant contributions regarding the clinical and basic aspects of the disease and more recently, in the development of therapeutic modalities for ADPKD. Nevertheless, the patient-oriented research on ADPKD is at a critical stage,

reflecting the fragmented experiences in diagnosis and care. Many questions still remain concerning the role of molecular genetic tools in the diagnosis, prognosis and management of the disease; the importance of dietary factors and identification and modification of risk factors or lifestyles in delaying the progression of the disease; the prevention, evaluation and management of renal and extrarenal manifestations; the optimal management of ESRD in this population; and patient support. Although increasing knowledge of its basic biology leads to identification of novel targets, the outcomes of recent trials and the rejection of kidney volume as a primary endpoint for clinical trials carry the risk to demotivate pharmaceutical companies. The public funding dedicated to ADPKD remains highly variable across the globe despite the significant progress made in the understanding on the clinical, genetic and mechanistic aspects of this disease.

ADPKD ranks 4th as a global cause for renal replacement therapy and thus it is a major genetic disorder of critical importance in nephrology. Although there are interests in investigating specific clinical aspects of the care of ADPKD patients, a global, independent academic network to increase ADPKD awareness, standardize the medical approach for such patients, identify knowledge gaps and promote practical integrated patient support is still lacking.

CONFERENCE OVERVIEW

The scope of this KDIGO conference is to gather a global panel with multi-disciplinary clinical expertise that will identify key issues relevant to the progression factors, mortality, co-morbidity, as well as patient support and health economical issues of ADPKD. The objective of this conference is to assess our current state of knowledge related to the evaluation, management and treatment of ADPKD, to summarize the outstanding knowledge gaps, and to propose a research agenda to resolve standing controversial issues. It is hoped that this conference will serve to inform whether there is sufficient evidence base for the development of a guideline on this topic and help pave the way to harmonize and standardize the care of ADPKD patients.

Drs. Vicente E. Torres (Mayo Clinic, USA) and Olivier Devuyst (University of Zurich, Switzerland) will co-chair this conference. The format of the conference will involve topical plenary presentations followed by focused discussion groups that will report back to the full group for consensus-building. Invited participants and speakers will include worldwide leading ADPKD experts and patient representatives who will address key clinical issues and the utility of patient-reported outcome measures as outlined in the Appendix: Scope of Coverage. The conference output will include publication of a position statement that will help guide KDIGO and others on additional research and ultimately the development of clinical practice guidelines.

References

1. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet 369: 1287-301, 2007.
2. Grantham JJ, Torres VE, Chapman AB, et al. Volume Progression in Polycystic Kidney Disease. N Engl J Med 354(20): 2122-30, 2006.
3. Chapman A, Johnson A, Gabow P, Schrier R. The renin-angiotensin-aldosterone system and autosomal dominant polycystic kidney disease. N Engl J Med 323(16): 1091-6, 1990.
4. Rizk D, Jurkovitz C, Veledar E, et al. Quality of life in autosomal dominant polycystic kidney disease patients not yet on dialysis. Clin J Am Soc Nephro 4(3): 560-6,2009.
5. Franz KA, Reubi FC. Rate of functional deterioration in polycystic kidney disease. Kidney Int 23(3): 526-9, 1983.
6. Lentine KL, Xiao H, Machnicki G, et al. Renal function and healthcare costs in patients with polycystic kidney disease. Clin J Am Soc Nephrol 5(8): 1471-9, 2010.
7. The European Polycystic Kidney Disease Consortium. The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. Cell 77: 881–894, 1994.
8. Hughes J, Ward CJ & Peral B et al. The polycystic kidney disease 1 (PKD1) gene encodes a novel protein with multiple cell recognition domains. Nat Genet 10: 151–160, 1995.
9. Polycystic kidney disease: the complete structure of the PKD1 gene and its protein. The International Polycystic Kidney Disease Consortium. Cell 81(2):289-98, 1995.
10. Mochizuki T, Wu G & Hayashi T et al. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. Science 272: 1339–1342, 1996.
11. Chapman AB, Bost JE, Torres VE, et al. Kidney Volume and Functional Outcomes in Autosomal Dominant Polycystic Kidney Disease. Clin J Am Soc Nephrol 7:479-86, 2012.
12. Serra AL, Poster D, Kistler AD, et al. Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. N Engl J Med 363(9):820-9, 2010.

13. Walz G, Budde K, Mannaa M, et al. Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease. N Engl J Med 363(9):830-40, 2010.

14. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. N Engl J Med 367:2407-18, 2012.

15. Ruggenenti P, Remuzzi A, Ondei P, et al. Safety and efficacy of long-acting somatostatin treatment in autosomal dominant polcysytic kidney disease. Kidney Int 68:206-16, 2005.

16. van Keimpema L, Nevens F, Vanslembrouck R, et al. Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. Gastroenterology 137:1661-8 e1-2, 2009.

17. Hogan MC, Masyuk TV, Page LJ, et al. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. J Am Soc Nephrol 21:1052-61, 2010.

18. Caroli A, Perico N, Perna A, et al. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. Lancet 382(9903):1485-95, 2013.

19. Chapman AB, Torres VE, Perrone RD, et al. The HALT polycystic kidney disease trials: design and implementation. Clin J Am Soc Nephrol 5:102-9, 2010.

20. Torres VE, Grantham JJ, Chapman AB, et al. Potentially Modifiable Factors Affecting the Progression of Autosomal Dominant Polycystic Kidney Disease. Clin J Am Soc Nephrol 6(3):640-7, 2011.

21. Gronwald W, Klein MS, Zeltner R, et al. Detection of autosomal dominant polycystic kidney disease by NMR spectroscopic fingerprinting of urine. Kidney Int 79(11):1244-53, 2011.

22. Kistler AD, Mischak H, Poster D, et al. Identification of a unique urinary biomarker profile in patients with autosomal dominant polycystic kidney disease. Kidney Int 76(1):89-96, 2009.

23. Meijer E, Bakker SJ, van der Jagt EJ, et al. Copeptin, a surrogate marker of vasopressin, is associated with disease severity in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol 6(2):361-8, 2011.

APPENDIX: SCOPE OF COVERAGE

A. Diagnosis

- Revision of diagnostic criteria
- Role of next generation sequencing and advancing technology
- Role of genetic testing for disease management
- Prevalence of ADPKD
- Pre-implantation genetic diagnosis
- Presymptomatic family/children screening

B. Management of hypertension and renal function decline

- Kidney volume as a prognostic biomarker
- Kidney volume as a surrogate endpoint
- Role of biomarkers in patient management
- What is the optimal treatment for hypertension?
- Role of hydration
- Control of risk factors other than hypertension
- Are renal outcomes (age at ESRD) improving?
- The role of total kidney volume, blood pressure and left ventricular mass in children with ADPKD

C. Management of renal manifestations

- Imaging and clinical diagnosis of renal cyst infection
- Management of renal cyst infection and other complicated infections (e.g. emphysematous pyelonephritis)
- Interventional and non-interventional treatment of nephrolithiasis
- Management of renal hemorrhagic complications
- Renal cell carcinoma in ADPKD
- Diagnosis/Management of chronic renal pain

D. Management of ESRD in ADPKD

- Choice of dialysis modality
- Need to monitor native kidneys after initiation of renal replacement therapy
- Timing of pre-emptive renal transplantation
- Evaluation of the ADPKD transplant candidate
- Evaluation of the ADPKD living related donor
- Choice of immunosuppression
- New-onset diabetes after transplantation
- Indications and timing of native nephrectomy

E. Management of extra-renal complications

- Evidence for environmental factors affecting polycystic liver disease (PLD)
- Imaging and clinical diagnosis of cyst infection
- Optimal management of cyst infection
- Management of patients with recurrent ascending cholangitis
- Role of interventional therapies to treat symptomatic PLD
- Role of liver transplantation
- Role of somatostatin analogs
- Screening for intracranial aneurysms
- Management of asymptomatic intracranial aneurysms
- Should we screen for other rare PKD complications such as valvular abnormalities, bronchiectasis, pericardial effusion?
- Management of vascular complications such as aortic aneurysms; should we screen; is there a familial risk?
- Comment on seminal vesicle cysts/infertility in ADPKD
- Contraception

F. Practical integrated patient support

- Psycho-social support
- Dietary guidance (from diagnosis to dialysis)
- Pain management
- Lifestyle and recreational adaptations
- Genetic counselling/family planning
- Patient financial implications (covering work/career, insurance)
- Enabling patient empowerment and self-management
- Benefits and feasibility of an ADPKD patient reported outcome measures (PROM) tool
- If no guidelines are foreseen in the short-term, can we publish an interim practical checklist - one for doctors and one for patients (or careers/representatives)?