

World Kidney Day 2008: Think Globally, Speak Locally

Connie L. Davis,* William E. Harmon,[†]
Jonathan Himmelfarb,[‡] Thomas Hostetter,[§]
Neil Powe,^{||} Paul Smedberg,[¶] Lynda A. Szczech,^{**}
and Peter S. Aronson for the American Society of
Nephrology Public Policy Board^{††}

*Department of Medicine, University of Washington, Seattle, Washington; [†]Department of Pediatric Nephrology, Children's Hospital, Boston, MA; [‡]Division of Nephrology, Maine Medical Center, Portland, Maine; [§]Department of Medicine, Albert Einstein College of Medicine, New York, New York; ^{||}Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins School of Medicine, Baltimore, Maryland; [¶]American Society of Nephrology, Washington, DC; ^{**}Duke University, Durham, North Carolina; and ^{††}Department of Medicine-Nephrology, Yale School of Medicine, New Haven, Connecticut

J Am Soc Nephrol 19: 413–416, 2008.
doi: 10.1681/ASN.2008010070

Thursday, March 13, 2008 will mark the third iteration of World Kidney Day (WKD). The concept of an annual WKD was first proposed in 2003 and, through a joint collaboration between the International Federation of Kidney Foundations and the International Society of Nephrology, the first WKD was launched on March 7, 2006. The primary goal for WKD is to draw attention to a global pandemic of kidney disease, with its associated morbidity and mortality, primarily resulting from amplification of cardiovascular risk. The concept of WKD has caught on remarkably quickly, resonating throughout the kidney disease community worldwide, thereby providing an energizing focus for efforts to squarely place kidney disease into a global public health framework. This year, it is anticipated that kidney organizations in at least 60 countries will participate by organizing health screening events, public lectures, press conferences, political activities, and other efforts to better inform primary care physicians, allied health professionals, individuals and families with kidney disease, as well as government health officials about the burgeoning importance of kidney disease.

The WKD concept stems directly from recent efforts to develop a simple, clinically relevant definition for chronic kidney disease (CKD). Before 2000, a consensus-driven, consistent definition of CKD did not exist.¹ Since that time, na-

tional and international consensus groups have arrived at consensus definitions of CKD and issued clinical practice guidelines and position statements related to a standardized definition.^{2,3} The development of these standardized definitions for CKD helps reveal that kidney disease is not just a relatively infrequent but individually costly disease, particularly, end-stage renal disease (ESRD). But in truth, ESRD is a highly prevalent disease with high collective costs and important public health consequences. WKD emphasizes kidney disease as “common, harmful, and treatable” with a consequent impetus on kidney disease screening, detection, surveillance, prevention, and research.^{4,5}

What should nephrologists be doing on WKD 2008? We think, as others have suggested,^{6–8} that this is an opportunity to simultaneously reflect on the past and look toward the future. The profession of nephrology is in the midst of a vital transformation, and the changing medical, social, public health, and political environments surrounding kidney disease will change the practice of nephrology.⁹ We think that, while reflecting on the many conundrums demanding attention concerning the epidemic of CKD, it is important for nephrologists to actively participate in the resultant medical, social, and political processes with a fundamental goal of improving outcomes for patients with kidney disease. Thus, WKD 2008 is a call to action for nephrologists in the United States and worldwide.

THINKING GLOBALLY

Beginning in 2005, the World Health Organization (WHO) has emphasized the importance of controlling chronic non-communicable diseases as a neglected global health priority.¹⁰ The WHO estimates that chronic diseases were responsible for more than 60% (35 million) of all deaths in 2005, with more than 80% of these deaths occurring in low income and middle income countries. More recently, in a study of 23 selected low income and middle income countries, chronic diseases are responsible for 50% of the total disease burden in 2005.¹¹ Lost economic productivity in these 23 countries from heart disease, stroke, and diabetes alone is estimated to be 84 billion U.S. dollars between 2006 and 2015. As a consequence, the WHO has targeted a 2% annual reduction in chronic disease death rates over the next 10 yr, which would avert 24 million deaths and save an estimated 8 billion dollars in these countries alone. The primary targets on a global level for intervention are the common causes of the major chronic diseases, which include unhealthy diet, excessive energy intake, physical inactivity, and tobacco use. Of note, these important modifiable risk factors have also been implicated in the development and progression of CKD.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Jonathan Himmelfarb, Maine Medical Center, 22 Bramhall Street, Portland, ME 04102; Phone: 207-871-2417; Fax: 207-871-6306; E-mail: himmej@mmc.org

Copyright © 2008 by the American Society of Nephrology

It is of interest to note that the WHO does not list CKD when evaluating the major chronic diseases from a global perspective.¹⁰ The WHO focuses on cardiovascular disease, cancer, chronic respiratory diseases, and diabetes as modifiable causes of projected global deaths from chronic disease. Nonetheless, CKD is a global health problem. In the United States, the prevalence of chronic CKD in adults may be as high as 13.1% of the population.¹² Although detailed, population-based data from the rest of the world are less available, studies from Europe, Asia, and worldwide also support a high prevalence of CKD as well as CKD-associated cardiovascular morbidity and mortality.^{13–15} Furthermore, throughout the world, the prevalent use of renal replacement therapy and the cost of providing kidney transplantation and dialysis continue to escalate.¹⁶ The Kidney Disease Improving Global Outcomes, a not-for-profit foundation whose stated mission is to improve the care and outcomes of patients with kidney disease worldwide, recommends that the government should adopt a public health policy for CKD, an activity that can be catalyzed on WKD.¹⁷

THINKING NATIONALLY

The most robust available epidemiologic data on the public health consequences of kidney disease emanates from the United States. Available data from the U.S. Renal Data System, and from nationally representative surveys, such as the National Health and Nutrition Examination Surveys, clearly establish the disease burden from CKD as a public health threat.¹⁸ In particular, CKD is highly prevalent, is associated with increased morbidity and mortality and healthcare costs, and disproportionately affects minorities and disadvantaged individuals. Furthermore, preventive strategies, including rigorous blood pressure control with the use of inhibitors of the renin-angiotensin system, can reduce the burden of kidney disease.¹⁹ Data are especially compelling with respect to subpopulations. A particular concern is the burden of CKD in the black population in the United States, where transition from moderate CKD to ESRD occurs at a threefold higher rate than is seen in white patients with CKD.^{20,21} Also of concern is the older-age population, where the prevalence of CKD is increased and who constitutes the fastest growing segment of the ESRD population.^{12,22}

That there are health consequences to having CKD is nearly indisputable. As has recently been noted,²³ CKD is associated with higher rates and faster progression of cardiovascular disease, stroke, overall mortality, and increased mortality, in the ICU setting, after coronary revascularization and after acute decompensated heart failure.^{24–27} Despite these robust epidemiologic data, there remain many gaps in our understanding of best clinical practice for patients with CKD, which can provide important research opportunities. Even from available epidemiologic data, it is not clear that individuals with diminished glomerular filtration rate (GFR) without the presence of

hypertension or diabetes truly have a significantly increased cardiovascular risk, nor is it clear from interventional trial data that screening for low GFR or microalbuminuria will identify subjects who can undergo successful secondary cardiovascular risk reduction in the absence of other cardiovascular risk factors, such as diabetes mellitus and hypertension. It is also not clear how much of the diminished GFR found in the elderly is caused by parenchymal kidney disease as opposed to the natural effects of aging on kidney function. Finally, and perhaps most important, the evidence base from randomized clinical trials to support interventions in the CKD population has been woefully inadequate to date.^{23,28} Clinical studies evaluating novel therapeutic approaches to arresting the progression of kidney disease are desperately needed.²⁹ Indeed, our therapeutic tools, although proven effective, remain limited in number. Thus, as has recently been noted,³⁰ it is important for the public policy aspects of CKD not to get ahead of the available data, so as not to risk credibility for the nephrology profession. Further research is key.

At the helm of kidney disease treatment is and must be the nephrologist, who must steer through a complex comprehensive treatment program. However, the nephrologist providing CKD care is acting in the context of many other changes in nephrology clinical practice. These changes include impending implementation of payment for quality programs, trends toward consolidation of the dialysis industry, and bundling of payment for dialysis services.⁹ Furthermore, although perhaps stabilizing, the incidence of ESRD increases faster than the prevalence of CKD.³¹ Application of our tools to treat CKD likely has contributed to the recent stabilization of the incidence of ESRD after decades of rapid growth, albeit at an unacceptably high number of 100,000 people per year. However, the arrival of the baby boom generation at the typical age for ESRD may reverse this trend unless strenuous efforts are applied. That there are too few nephrologists for the growing numbers of patients with ESRD has been well documented.³² New U.S. Renal Data System projections estimate more than 500,000 persons on dialysis by 2020 with an additional 250,000 living with a transplant.²² Although this issue has received attention, without action this will continue to become a greater problem in the upcoming decade with implications for both the quality and cost of care.

ACTING LOCALLY

People with CKD are largely unaware that they have reduced kidney function. Among those with an estimated GFR less than 30 ml/min per 1.73 m², fewer than one half knew that they had kidney disease.¹² The shockingly low proportions of people with kidney disease who are aware of their kidney disease (<20% in all strata of GFR)³³ indicates that there is still major room for improvements in secondary prevention. Can we be so bold as to expect that a truly effective national program might result in a decrease in incident ESRD? Efforts to improve this

situation are continuing, focusing largely on people at highest risk and their primary care providers. Nephrologists can play a major role, particularly by providing formal and informal public education to primary care colleagues (including general internist, family physicians, nurse practitioners, physician assistants, and diabetes educators). The American Society of Nephrology has developed a PowerPoint slide set that can be obtained at our website (<http://www.asn-online.org>). This set is useful for local presentations to general medical audiences such as Medical Grand Rounds, which may be the most important activity for nephrologists on WKD.

Public education should continue to focus on fundamental concepts that are the cornerstone of the detection of kidney disease. As simple as the message sounds, the most important service that American Society of Nephrology members can provide is to advise primary care providers that two simple tests can detect almost all CKD. The estimated GFR and a urine albumin-to-creatinine ratio provide adequate testing.³⁴ Nephrologists are best suited to helping the primary care provider determine who should be tested and how to interpret screening tests. It is already recommended that persons with diabetes be tested yearly for the presence of CKD.³⁴ Testing hypertensives also seems cost-effective.³⁵ Finally, because CKD is common among relatives of persons with ESRD and increases mortality in cardiovascular disease, many call for testing in these groups as well.³⁶ Nephrologists are well positioned to encourage their local laboratories to provide estimated GFRs with serum creatinine. Material explaining the rationale and steps for the laboratory may be obtained at the National Kidney Disease Education Program web site (<http://nkdep.nih.gov>). Laboratory directors generally are very responsive to nephrologists' requests, and now nearly one half of clinical laboratories provide this service. Nephrologists should encourage all laboratories to do so.

On WKD in 2008, each nephrologist should consider how he/she can contribute to an increase in the local screening, identification, and treatment efforts for kidney disease. Each nephrologist needs to help disseminate information on best practices for primary care providers in their referral base. As a profession, we need to work to evolve processes for efficient care patterns. This will not only improve our patients' quality of lives but may also attract young physicians to the practice of nephrology. Nephrologists must also rededicate efforts and become increasingly involved, both locally and nationally, in advocacy for the importance of kidney disease, and in the redesign of kidney disease care models across the entire spectrum of disease severity. Finally, nephrologists across the country should be strong advocates for enhanced support from the National Institutes of Health for research on the causes and treatment of CKD.

DISCLOSURES

None.

REFERENCES

- Hsu CY, Chertow GM: Chronic renal confusion: insufficiency, failure, dysfunction, or disease. *Am J Kidney Dis* 36: 415–418, 2000
- Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, Nahas ME, Jaber BL, Jadoul M, Levin A, Powe NR, Rossert J, Wheeler DC, Lameire N, Eknoyan G: Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 67: 2089–2100, 2005
- Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation: National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 139: 137–147, 2003
- Levey AS, Andreoli SP, DuBose T, Provenzano R, Collins AJ: CKD: common, harmful, and treatable—World Kidney Day 2007. *Am J Kidney Dis* 49: 175–179, 2007
- Collins AJ, Couser WG, Dirks JH, Kopple JD, Reiser T, Riella MC, Robinson S, Shah SV, Wilson A: World Kidney Day: an idea whose time has come. *J Am Soc Nephrol* 17: 600–601, 2006
- Kiberd B: The chronic kidney disease epidemic: stepping back and looking forward. *J Am Soc Nephrol* 17: 2967–2973, 2006
- Shah SV, Feehally J: The third World Kidney Day: looking back and thinking forward. *Nat Clin Pract Nephrol* 4: 1, 2008
- Eknoyan G: Kidney disease: wherefore, whence, and whereto? *Kidney Int* 71: 473–475, 2007
- Himmelfarb J, Berns A, Szczech L, Wesson D: Cost, quality, and value: the changing political economy of dialysis care. *J Am Soc Nephrol* 18: 2021–2027, 2007
- World Health Organization: *Preventing Chronic Diseases: A Vital Investment*. Geneva, Switzerland, World Health Organization, 2005, http://www.who.int/chp/chronic_disease_report/contents/en/index.html
- Abegunde DO, Mathers CD, Adam T, Ortegón M, Strong K: The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet* 370: 1929–1938, 2007
- Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS: Prevalence of chronic kidney disease in the United States. *JAMA* 298: 2038–2047, 2007
- Eknoyan G, Lameire N, Barsoum R, Eckardt KU, Levin A, Levin N, Locatelli F, MacLeod A, Vanholder R, Walker R, Wang H: The burden of kidney disease: improving global outcomes. *Kidney Int* 66: 1310–1314, 2004
- Rao M, Pereira BJ: Chronic kidney disease in India: a hidden epidemic. *Indian J Med Res* 126: 6–9, 2007
- Li PK, Weening JJ, Dirks J, Lui SL, Szeto CC, Tang S, Atkins RC, Mitch WE, Chow KM, D'Amico G, Freedman BI, Harris DC, Hooi L, De Jong PE, Kincaid-Smith P, Lai KN, Lee E, Li F, Lin S, Lo W, Mani MK, Mathew T, Murakami M, Qian J, Ramirez S, Reiser T, Tomino Y, Tong MK, Tsang W, Tungsanga K, Wang H, Wong AK, Wong KM, Yang W, De Zeeuw D, Yu AW, Remuzzi G, on Behalf of the Participants of ISN Consensus Workshop on Prevention of Progression of Renal Disease: A report with consensus statements of the International Society of Nephrology 2004 Consensus Workshop on Prevention of Progression of Renal Disease, Hong Kong, June 29, 2004. *Kidney Int Suppl* 94: S2–S7, 2005
- Lysaght MJ: Maintenance dialysis population dynamics: current trends and long-term implications. *J Am Soc Nephrol* 13(Suppl 1): S37–S40, 2002
- Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, Nahas ME, Jaber BL, Jadoul M, Levin A, Powe NR, Rossert J, Wheeler DC, Lameire N, Eknoyan G: Chronic kidney disease as a global public health problem: approaches and initiatives. A position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 72: 247–259, 2007
- DuBose TD Jr: American Society of Nephrology Presidential Address 2006. Chronic kidney disease as a public health threat: new strategy for a growing problem. *J Am Soc Nephrol* 18:1038–1045, 2007
- Schoolwerth AC, Engelgau MM, Hostetter TH: A public health action

- plan is needed for chronic kidney disease. *Adv Chronic Kidney Dis* 12: 418–423, 2005
20. Krop JS, Coresh J, Chambless LE, Shahar E, Watson RL, Szklo M, Brancati FL: A community-based study of explanatory factors for the excess risk for early renal function decline in blacks vs whites with diabetes: the Atherosclerosis Risk in Communities study. *Arch Intern Med* 159: 1777–1783, 1999
 21. Tarver-Carr ME, Powe NR, Eberhardt MS, LaVeist TA, Kington RS, Coresh J, Brancati FL: Excess risk of chronic kidney disease among African-American versus white subjects in the United States: a population-based study of potential explanatory factors. *J Am Soc Nephrol* 13: 2363–2370, 2002
 22. U.S. Renal Data System. *USRDS 2007 Annual Data Report: Atlas of End-stage Renal Disease in the United States*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2007.
 23. Novak JE, Szczech LA: Feast and famine: epidemiology and clinical trials in chronic kidney disease. *J Am Soc Nephrol* 19: 2–4, 2008
 24. Vanholder R, Massy Z, Argiles A, Spasovski G, Verbeke F, Lameire N; European Uremic Toxin Work Group: Chronic kidney disease as cause of cardiovascular morbidity and mortality. *Nephrol Dial Transplant* 20: 1048–1056, 2005
 25. Clermont G, Acker CG, Angus DC, Sirio CA, Pinsky MR, Johnson JP: Renal failure in the ICU: comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes. *Kidney Int* 62: 986–996, 2002
 26. Ix JH, Mercado N, Shlipak MG, Lemos PA, Boersma E, Lindeboom W, O'Neill WW, Wijns W, Serruys PW: Association of chronic kidney disease with clinical outcomes after coronary revascularization: the Arterial Revascularization Therapies Study (ARTS). *Am Heart J* 149: 512–519, 2005
 27. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J; ADHERE Scientific Advisory Committee and Investigators: High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail* 13: 422–430, 2007
 28. Himmelfarb J: Chronic kidney disease and the public health: gaps in evidence from interventional trials. *JAMA* 297: 2630–2633, 2007
 29. Eddy AA, Neilson EG: Chronic kidney disease progression. *J Am Soc Nephrol* 17: 2964–2966, 2006
 30. Couser WG: Chronic kidney disease the promise and the perils. *J Am Soc Nephrol* 18: 2803–2805, 2007
 31. Hsu CY, Vittinghoff E, Lin F, Shlipak MG: The incidence of end-stage renal disease is increasing faster than the prevalence of chronic renal insufficiency. *Ann Intern Med* 141: 95–101, 2004
 32. Neilson EG, Hull AR, Wish JB, Neylan JF, Sherman D, Suki WN: The Ad Hoc Committee report on estimating the future workforce and training requirements for nephrology: the Ad Hoc Committee on Nephrology Manpower Needs. *J Am Soc Nephrol* 8(suppl): S1–S4, 1997
 33. Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, Hostetter TH: Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. *J Am Soc Nephrol* 16: 180–188, 2005
 34. Vassalotti JA, Stevens LA, Levey AS: Testing for chronic kidney disease: a position statement from the National Kidney Foundation. *Am J Kidney Dis* 50: 169–180, 2007
 35. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR: Screening for proteinuria in US adults: a cost-effectiveness analysis. *JAMA* 290: 3101–3114, 2003
 36. McClellan W, Speckman R, McClure L, Howard V, Campbell RC, Cushman M, Audhya P, Howard G, Warnock DG: Prevalence and characteristics of a family history of end-stage renal disease among adults in the United States population: Reasons for Geographic and Racial Differences in Stroke (REGARDS) Renal Cohort Study. *J Am Soc Nephrol* 18: 1344–1352, 2007

ARPKD and ADPKD: First Cousins or More Distant Relatives?

Jun-ya Kaimori* and Gregory G. Germino*[†]

*Division of Nephrology, [†]Departments of Medicine and Molecular Biology and Genetics, Johns Hopkins University School of Medicine, Baltimore, Maryland

J Am Soc Nephrol 19: 416–418, 2008.
doi: 10.1681/ASN.2008010033

Superficially, autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) seem to be more different than alike. ADPKD is common, its cysts arise from any nephron segment, and it is slowly progressive.¹ Hepatic cysts are its primary extrarenal lesion. The disease results from mutation of either of two genes, *PKD1* and *PKD2*, that encode distinct proteins (PC1 and PC2) that form a receptor-channel complex. In sharp contrast, ARPKD is 20-fold less common, presents primarily in infancy and childhood, and is typically more severe.² Affected newborns are often born with massively enlarged, cystic kidneys and die in the perinatal period from respiratory failure. Unlike in ADPKD, these cystic kidneys retain their reniform shape and the cysts are fusiform dilations mainly of the collecting ducts. A variety of liver abnormalities that result from ductal plate malformations are universally present. The disease results from mutation of *PKHD1*, a novel gene that encodes a cell-surface receptor or ligand.^{3,4}

Despite these differences, there are several indirect lines of evidence to suggest that the diseases may be more related than previously suspected. First, there are occasional cases that present with overlapping clinical features.^{5,6} Second, we now know that ADPKD is recessive on a molecular level,⁷ with its two-hit mechanism explaining some of the clinical differences between it and ARPKD. In fact, mice homozygous for a hypomorphic missense change of *Pkd1* develop severe cystic disease restricted to distal nephron segments that is remarkably like that seen in human ARPKD.⁸ Third, the proteins encoded by each locus have been co-localized to the primary cilium, a structure widely believed to be critically involved in tubular luminal regulation.⁹ Fourth, ADPKD and ARPKD cystic epithelia are reported to have similar abnormalities with respect to cAMP-mediated signaling, with inhibitors of the vasopressin receptor equally effective in *Pkhd1* and *Pkd2* cystic mouse models.^{10,11}

Four recent studies provided more direct evidence linking the two disorders. Two groups independently reported that PC2 forms a complex with fibrocystin/polyductin (FPC),^{12,13} possibly

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Gregory G. Germino, Ross 958, 720 Rutland Avenue, Baltimore, MD 21205. Phone: 410-614-1650; Fax: 410-614-5129; E-mail: ggermino@jhmi.edu

Copyright © 2008 by the American Society of Nephrology