Chronic Kidney Disease—The Promise and the Perils

William G. Couser

Editor Emeritus, Belding H. Scribner Professor of Medicine (retired), University of Washington, Seattle, Washington

J Am Soc Nephrol 18: 2803–2805, 2007. doi: 10.1681/ASN.2007080964

In recent weeks I had the pleasure of participating in three meetings devoted to the general topic of chronic kidney disease (CKD). The first, a satellite symposium of the World Congress of Nephrology, was titled "The Cardiovascular System in Chronic Kidney Disease" and was held in Buzios, Brazil; the second, the inaugural "Asian Forum on CKD," was organized by the Japanese Society of Nephrology in Hamamatsu, Japan; and the third, the "CKD Scientific Forum," was held in Baltimore, Maryland, and was organized by the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases, an enlightened effort to bring together leaders of societies, journals, and research groups to exchange ideas and enhance collaboration around CKD. The energy at all of these events was high, very high. Indeed, one had the sense of standing in a tunnel in which the velocity of the wind makes it difficult to hear or avoid being blown along in the ongoing maelstrom of activity related to CKD and virtually impossible to stop and actually look around into which direction one is being blown. However, it is my perception that we are not yet exactly where we need to be with respect to CKD, and because of that there is risk that someone may downplay or even debunk the most important concept the nephrology community has generated in the past two decades. So I think it is time we sit back and think a bit more carefully about what we are saying and where we are going with CKD. The reasons are several.

First, let me acknowledge that CKD has provided a windfall of attention to, and increased awareness of renal disease, something "thought leaders" in our field have struggled to accomplish for decades with little previous success.[1] Clinical nephrology during the latter half of the 20th century was a niche subspecialty focused largely on renal replacement therapy, dialysis, and transplantation. Although these are life-saving treatments, they are extremely costly and relevant only to less than 0.2% of the population.

With the advent of CKD and the "new nephrology," renal disease has now become a health issue for about 10% of the population of most countries.[2–4] Moreover, the marked increase in risk of cardiovascular disease associated with CKD,[5] and the potential to prevent it through early detection and treatment,[6] now places the kidney at center stage in the battle against the largest cause of premature mortality worldwide. The message we are sending is very loud and clear: "We are facing an epidemic of CKD, and with it an epidemic of cardiovascular disease, which can be detected early and even prevented by appropriate emphasis on measurements of kidney function, particularly glomerular filtration rate (GFR) and microalbuminuria". There is no doubt that being on center stage is much more exciting than being in the wings, and the current velocity of the wind in the CKD tunnel reflects that. But with a position on center stage in any arena comes a level of scrutiny that nephrology has not often had before, and with it a responsibility to be prepared for a much more intense examination of what we are saying. Let me mention a few concerns.

Excitement is always generated by something new. The observation that 10% of the population has CKD is new—and therefore exciting. But is it really new? We have known for half a century there is a spectrum of renal function in the general population ranging from "normal" levels to near zero, and this continuous spectrum follows a bell-shaped curve with movement to the left with aging.[7] The contribution of the Kidney Disease Outcomes Quality Initiative (KDOQI) by the United States National Kidney Foundation was to break this continuous spectrum down into several separable ranges of GFR and to identify each range as a "stage" of CKD.[8] That concept has gained enormous traction and served as an extremely useful tool to drive research on the epidemiology of renal insufficiency and its associated consequences. It also provides a universal language that allows data from one source to be shared and compared with data from another. But it has limitations of which we must remain cognizant. First, defining different segments of a continuous distribution as separate stages of a disease process has not created anything new. The data are old; only the packaging is new.

Second, the staging of CKD implies that otherwise healthy people with GFR values <60 ml/min (or even <90 ml/min if one is a purist and includes "stage II" CKD) have a "disease." The semantics and rationale for using the term "disease" to characterize these levels of renal function have been eloquently discussed.[9] But in fact, aside from redefining the terminology, we do not know that many of these individuals have a disease. To date there is no reliable source of information on the underlying renal pathology in early CKD, nor is there compelling evidence that many of these people have anything intrin-

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

Correspondence: Dr. William G. Couser, 16050 169th Avenue NE, Woodinville, WA 98072. Phone: 206-890-4583; Fax: 425-488-5489; E-mail: wgc@u.washington.edu

sically wrong with their kidneys other than a less than optimal level of function and/or some microalbuminuria. Maybe, for example, these individuals didn't fully benefit from fetal programming the way most of us did.[10]

Third, identification of stages of CKD implies, perhaps unintentionally, that CKD is a progressive process with those afflicted moving eventually from earlier to more advanced stages of disease. Although this clearly happens in many patients with defined forms of kidney disease like diabetes and glomerulonephritis, there is a paucity of data documenting such progression in patients with CKD defined *only* as a GFR <60 ml/min or with microalbuminuria. Indeed, it is clear from several studies that many such patients do not progress over several years of follow-up.[11,12]

There are other issues, too, including the much-discussed and -analyzed problems associated with the usual GFR measurement equations,[13] as well as the applicability of the stages defined by US data to other populations (almost 20% of healthy Japanese individuals would have stage 3 CKD calculated by the conventional Modification of Diet in Renal Disease (MDRD) equation (GFR <60 ml/min),[12] accompanied by the impending proliferation of "correction factors" for different populations.[14,15] And there is the question of whether it is really credible to identify otherwise healthy elderly with reduced GFR values, which may be present in up to 50%, as victims of CKD.[16] Almost certainly the number of people with a kidney "disease," as disease is conventionally defined, is much less than 10% of the adult population. There are doubtless ways to estimate this more accurately, but that is not the purpose of my comments.

What has really put CKD on the public health map is not the fact that it afflicts such a large proportion of the population but the recognition that it is linked to a markedly increased risk of cardiovascular disease, so much so that people suffering from CKD are up to 100 times more likely to die of cardiovascular disease than to ever require renal replacement therapy.[17] Small decrements in GFR and levels of albumin excretion even within the "normal" range are linked to increased cardiovascular risk.[17] Again, the implication is that this observation is new and therefore especially alarming, particularly because it appears that therapy directed at the kidney may be able to reduce the incidence of cardiovascular disease.[18] But again, caution is warranted.

Most studies to date implicating CKD as a major risk factor for cardiovascular disease are done in cohorts that include significant numbers of patients with hypertension or diabetes and often both. The observation that patients with hypertension and diabetes are at increased risk of cardiovascular disease is hardly new, nor is it new that control of these conditions reduces risk. Do patients with a GFR <60 ml/min who do *not* have hypertension or diabetes actually have a significantly increased risk of cardiovascular disease? We still do not know the answer to that question. Although there are ways to adjust data for effects of these confounding variables using regression models, these adjustments generally do not account for severity or substitute for real data obtained by following real patients. What proportion of patients with incident cardiovascular disease has CKD (independent of diabetes and hypertension) and might have received successful preventive therapy if GFR or microalbuminuria had been measured earlier? We do not know the answer to that question either, although the issue is critical for making the economic case for early detection and prevention programs focused on the kidney.

Let me voice another concern here as well. One reason the CKD story has been so compelling, particularly that component of it related to microalbuminuria, is that it makes excellent pathophysiological sense to conceive the glomerular microvasculature as providing a unique window into the larger vascular system such that minor levels of vascular or endothelial dysfunction can be detected early because they result in increased leakage of albumin into the urine through glomerular microvessels where the physician, especially the nephrologist, can detect it and intervene to reduce further vascular damage before clinical manifestations develop.[19] But is this construct really true? Although there is an abundance of data on endothelial dysfunction in renal insufficiency,[10] to date the concept that it accounts for microalbuminuria in humans or is related to cardiovascular disease is only a hypothesis.

Verification of this hypothesis is complicated by the fact that the normal glomerular filtrate may contain upwards of 10 g of albumin per day, most of which is reabsorbed and not excreted.[20] Thus it would require only a trivial change in tubular function, independent of glomerular endothelial health, to account for the several hundred micrograms of albumin in the urine that we identify with CKD. There is little doubt from epidemiologic data that such an increase in albumin excretion does identify patients at risk for cardiovascular disease.[21,22] However, there is virtually no direct evidence that this represents a "window into the vascular system" rather than minor alterations in tubular function, a process that is much more difficult to conceive as reflecting early large vessel vascular disease. If the pathophysiological hypothesis underlying the case for microalbuminuria-defined CKD proves incorrect, the credibility of the entire effort will not be destroyed, but it will be impugned.

I want to end my observations with the obvious conclusion that much more research is needed before nephrology can make a really compelling case to the world of medicine and public health that increased attention to measures of renal function and albumin excretion can add substantially to what is already known about risk factors and prevention of cardiovascular and renal disease. But even that indisputable conclusion requires a caveat. Much of the data we are citing in support of our current concepts of CKD derive from complex statistical analysis of large, usually readily available, databases; National Health and Nutrition Evaluation Survey, United States Renal Data System, and the Framingham Study are examples. These analyses too often do not focus on verification of a new, biologically plausible hypothesis but rather rest on identifying independent and linked associations between numerous covariables that are available in the database to identify statistically significant associations from which a hypothesis then emerges to explain them. This process of "data dredging," to use a term coined in frustration by one of my former *JASN* Associate Editor colleagues, can be enormously productive. The principals of one of the major research groups presenting at the recent National Institutes of Health CKD conference proudly identified more than 500 publications generated by that particular study over several years. How many of these represented papers in high-quality, peer-reviewed journals that significantly advanced our understanding of CKD? Likely less than 5%.

For the next generation of young physician-scientists getting swept into clinical research by the challenges of CKD and the potential for generating many career-enhancing publications utilizing only manipulations of databases on a computer, it is important to recognize that there are still many very important and unanswered questions in the area of CKD. What is needed is not more publications derived from secondary analysis of existing databases, relevant as these may sometimes be, but rather hypothesis-driven studies that are designed prospectively to address many central questions about CKD that still lack answers.

The purpose of my thoughts is not to challenge the validity of what we are saying about CKD or to "puncture the CKD myth." Some of these concerns have been voiced in *JASN* before.[23] Rather, it is to point out that we face a serious risk in pursuing the media and public affairs aspect of a CKD campaign by getting ahead of our data. And for the nephrology research community, which is responsible for generating that data, we also face a need to look carefully at what the key unanswered questions in CKD are and how best to design studies to address them. If we do not do that, we are at high risk that CKD will remain only a nephrologic construct of marginal interest to the world of public health, or worse that someone outside nephrology will puncture the CKD myth for us. This would set back what is clearly one of the most promising opportunities nephrology has ever had to bring the fruits of our subspecialty to bear for the millions of patients worldwide that are likely to benefit from them.

DISCLOSURES

None.

REFERENCES

1. 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
2. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 41: 1–12, 2003
3. El Nahas ME: The global challenge of chronic kidney disease (Nephrology Forum). *Kidney Int* 68: 2918–2929, 2005
4. Couser WG: ISN and the 'new nephrology'. *Nat Clin Pract Nephrol* 2: 541, 2006
5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
6. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, de Zeeuw D, de Jong PE, van Veldhuisen DJ, van Gilst WH; Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators: Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* 110: 2809–2816, 2004
7. Smith H: *The Kidney: Structure and Function in Health and Disease.* New York, Oxford University Press, 1951
8. Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, de Zeeuw D, Hostetter TH, Lameire N, Eknoyan G: Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improve Global Outcomes (KDIGO). *Kidney Int* 67: 2089–2100, 2005
9. Eknoyan G: Kidney disease: Wherefore, whence, and whereto? *Kidney Int* 71: 473–475, 2007
10. Amann K, Wanner C, Ritz E: Cross-talk between the kidney and the cardiovascular system. *J Am Soc Nephrol* 17: 2112–2119, 2006
11. Viktorsdottir O, Palsson R, Aspelund T, Andresdottir MB, Gudnason V, Indridason OS. Progression of CKD in a population-based sample [Abstract]. *J Am Soc Nephrol* 2007, in press
12. Tomlinson LA, Holt SG, Rajkumar C. Measurements of arterial health are associated with adverse outcomes in CKD 3 and 4 [Abstract]. *J Am Soc Nephrol* 2007, in press
13. Coresh J, Stevens LA: Kidney function estimating equations: Where do we stand? *Curr Opin Nephrol Hypertens* 15: 276–284, 2006
14. Imai E, Horio M, Iseki K, Yamagata K, Watanabe T, Hara S, Ura N, Kiyohara Y, Hirakata H, Moriyama T, Ando Y, Nitta K, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S: Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. *Clin Exp Nephrol* 11: 156–163, 2007
15. Ying-Chun Ma, Li Zuo, Jiang-Hua Chen, Qiong Luo, Xue-Qing Yu, Ying Li, Jin-Sheng Xu, Song-Min Huang, Li-Ning Wang, Wen Huang, Mei Wang, Guo-Bin Xu, Hai-Yan Wang; on behalf of the Chinese eGFR Investigation Collaboration: Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 17: 2937–2944, 2006
16. Maaravi Y, Bursztyn M, Hammerman-Rozenberg R, Stessman J: Glomerular filtration rate estimation and mortality in an elderly population. *QJM* 100: 441–449, 2007
17. Keith D, Nicholls G, Guillion C, Brown JB, Smith DH: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 164: 659–663, 2004
18. Shulman NB, Ford CE, Hall WD, Blaufox MD, Simon D, Langford HG, Schneider KA: Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-Up Program Cooperative Group. *Hypertension* 13[Suppl]: I80–I93, 1989
19. Deckert T, Feldt Rasmussen B, Borch Johnsen K, Jensen T, Kofoed-Enevoldsen A: Albuminuria reflects widespread vascular damage: The Steno hypothesis. *Diabetologia* 32: 219–226, 1989
20. Russo LM, Sandoval RM, McKee M, Osicka TM, Collins AB, Brown D, Molitoris BA, Comper WD: The normal kidney filters nephrotic levels of albumin retrieved by proximal tubule cells: Retrieval is disrupted in nephrotic states. *Kidney Int* 71: 504–511, 2007
21. Arnlov J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, Benjamin EJ, D'Agostino RB, Vasan RS: Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: The Framingham Heart Study. *Circulation* 112: 969–975, 2005
22. Lambers Heerspink HJ, Brinkman JW, Bakker SJ, Gansevoort RT, de Zeeuw D: Update on microalbuminuria as a biomarker in renal and cardiovascular disease. *Curr Opin Nephrol Hypertens* 15: 631–636, 2006
23. Kiberd B: The chronic kidney disease epidemic: Stepping back and looking forward. *J Am Soc Nephrol* 17: 2967–2973, 2006