

World Kidney Day 2011: Protect Your Kidneys, Save Your Heart

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March 10, 2011, will mark the celebration of the sixth World Kidney Day, an annual event jointly sponsored by the International Society of Nephrology and the International Federation of Kidney Foundations. Since its inception in 2006, World Kidney Day has grown dramatically to become the most widely celebrated event associated with kidney disease in the world and the most successful effort to raise awareness among both the general public and government health officials about the dangers of kidney disease, especially chronic kidney disease (CKD).

In 2011, World Kidney Day will call attention to the large and often unappreciated role played by kidney dysfunction in increasing premature cardiovascular disease (CVD), the most common cause of morbidity and mortality worldwide (1). Can a focus on early detection and prevention of kidney disease really improve long-term cardiovascular health? In this editorial, convey the message that increased attention to the kidneys can indeed improve long-term health outcomes by reducing both kidney disease and CVD and should therefore be a central component of any global health strategy intended to reduce the enormous and growing burden of chronic NCDs.

CVD and the kidney

CVD is the most common of the chronic NCDs that affect global mortality. Approximately 30% of all deaths worldwide and 10% of all healthy life lost to disease are accounted for by CVD alone (1). Although there has been some decline in mortality from CVD in developed countries, no such decline has been reported in developing countries, in ethnic and socially disadvantaged minority populations, or in people with accompanying CKD (2,3).

The presence of CKD significantly increases the risk for a cardiovascular event in both diabetes and hypertension (4,5). However, less well appreciated is that CKD alone is a strong risk factor for CVD, independent of diabetes, hypertension, or any other conventional CVD risk factor (6,7). This is especially true when an increase in proteinuria, a major target of any CKD screening program, is present (6–9).

The 20- to 30-fold increase in CVD in patients with ESRD has long been recognized, but the increased risk for CVD associated with lesser degrees of renal functional impairment was definitively demonstrated only in 2004. Go *et al.* (6) reported an independent and

graded association between GFR and risk for death, cardiovascular events, and hospitalizations in a community-based study of more than 1000 individuals.

Is this dramatic increase in CVD risk associated with CKD really due to CKD, or does it just reflect the coexistent diabetes or hypertension that is present in a majority of these patients? The independent effect of CKD alone has now been well documented in many studies (7). The risk for cardiac death is increased 46% in people with a GFR between 30 and 60 ml/min (stage 3 CKD) independent of traditional cardiovascular risk factors, including diabetes and hypertension (10). The increased risk for cardiovascular events and mortality in people who are older than 55 years and have CKD alone is equivalent to or even higher than that seen in patients with diabetes or previous myocardial infarcts (11). Both general (6,12) and high-risk populations (13,14) exhibit an increased risk for CVD with CKD. This increased risk for CVD is not confined to the elderly: In volunteers with an average age of 45 years, the risk for myocardial infarct, stroke, and all-cause mortality was doubled in those with CKD (14).

Proteinuria and Cardiovascular Risk

In considering the value of recommending screening for CKD along with conventional CVD risk factors in selected individuals, data showing that the risk for CVD is better correlated with proteinuria (albuminuria) than with GFR alone is particularly relevant because proteinuria is virtually always a marker of kidney disease and is not a conventional CVD risk factor (6,8,9,15).

With regard to proteinuria as a predictor of later CVD, the Prevention of Renal and Vascular Endstage Disease (PREVEND) study showed a direct linear relationship between albuminuria and risk for cardiovascular death in the general population even at levels of albumin excretion generally considered within the “normal” range (15 to 29 mg/d) and was increased more than sixfold when albumin excretion exceeded 300 mg/d (8).

Recent data from the US National Health and Nutrition Examination Survey (NHANES) database as well as from Japan also document an independent effect of albuminuria on risk for both CVD and all-cause mortality at all levels of GFR (15,16). In patients with congestive heart failure but without diabetes,

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hypertension, or reduced GFR, increased urinary albumin predicts both cardiovascular and all-cause mortality (17). Similar results are obtained from patients with coronary disease or previous myocardial infarcts, in whom proteinuria conferred a greater risk for mortality than did reduced GFR, although both adversely affected outcomes (18).

Of interest, not only the likelihood but also the time to development of a cardiovascular event is accelerated significantly by the presence of proteinuria at all levels of GFR (19). In individuals who did not have diabetes, had normal serum creatinine levels, and underwent percutaneous coronary interventions, approximately 78% had demonstrable CKD when screened more stringently for renal function (estimated GFR, urine protein) (20). The presence of CKD not only is a likely factor in accelerating development of coronary disease in these patients but also has been associated with an increase in other risks, including hemorrhagic complications, contrast nephropathy, restenosis, and death (10). Thus, multiple studies now confirm that proteinuria is a graded risk factor for CVD independent of GFR, hypertension, and diabetes and that this risk extends down into ranges of albumin excretion generally considered "normal" (21,22). Moreover, this increased cardiovascular risk has been well demonstrated in several studies in which only dipsticks were used to screen for increased protein excretion (6,18,23).

Although there has been concern that CKD diagnosed by reduced GFR alone identifies predominately older adults at increased risk because of age alone (24), the connection between proteinuria as an independent risk factor for cardiovascular mortality has been confirmed by meta-analysis of 22 separate, general population, cohort studies and in both older (>65) and younger people of several nationalities and racial groups (23).

Can treatment of CKD reduce CVD?

Finally and most important, from a clinical perspective, provocative data suggest that renal-targeted interventions designed to reduce proteinuria and slow progression of CKD can reduce CVD risk as well. Angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers are of documented benefit in slowing progression of established diabetic and nondiabetic CKD (25–29). Of interest related to slowing progression, the incidence of CVD in CKD is significantly higher with more rapid loss of GFR independent of other risk factors, suggesting that interventions that slow progression may also reduce CVD (19). A 44% reduction in cardiovascular mortality during 4 years has been reported in patients screened from a general population who had no risk factors except increased albumin in the urine and were treated with renal-targeted ACEI therapy (30). This effect was seen primarily in people with albumin excretion rates of >50 mg/d in a pilot study, and the intervention was shown to be cost-effective in that population (31). Cardiovascular end points were sig-

nificantly reduced in direct proportion to the reduction of albuminuria with ACEI therapy, and albuminuria proved to be the only predictor of cardiovascular outcome (32). Other studies have also demonstrated that changes in proteinuria (in patients with diabetes) better predict outcomes than changes in BP achieved with ACEI therapy (33). The potential benefit of renal-targeted therapies has recently been highlighted by observations that higher dosages of renin-angiotensin system blockers than required for BP control alone can further reduce proteinuria independent of effects on BP or GFR and that addition of salt restriction or diuretics, both very inexpensive interventions, can further enhance the proteinuria-reducing effect of renin-angiotensin system blockade (34,35). Data are not yet available to establish that screening for CKD and subsequent interventions will reduce cardiovascular mortality and be cost-effective in younger people (<55) (36). However, it is now known that albuminuria is a better predictor of renal and cardiovascular events than BP alone, that reducing proteinuria is more renoprotective and cardioprotective than lowering BP alone, and that identification of CKD can improve cardiovascular outcomes.

Conclusions

As celebrations of the sixth World Kidney Day approach on March 10, 2011, it is worth noting that before the past decade, kidney disease was seen by most government and public health authorities as largely confined to patients with ESRD, thankfully a rare condition because the enormous cost of renal replacement therapy disproportionately consumes scarce health care resources and is well beyond the means of countries inhabited by more than 80% of the world's population (37,38). Much has changed. We now appreciate that kidney disease is not rare: Approximately 10% of the population has evidence of renal dysfunction. We know that these individuals are not of concern just because a few will progress to ESRD but more because they carry a greatly enhanced risk for premature death from CVD, the single largest and most expensive health care threat we confront at a global level (1). Just as progress is being made in treating most of the traditional cardiovascular risk factors, CKD has emerged as yet another one that causes substantial vascular toxicity independently. Fortunately, there is good news as well. Biomarkers of CKD (proteinuria, estimated GFR) are easy and relatively inexpensive to detect, and one of these, proteinuria, emerges early in the evolution of generalized vascular disease. Thus, kidney-targeted detection and prevention programs seem to offer a valuable opportunity to institute early preventive measures that go beyond traditional cardioprotective approaches. There is now compelling evidence that including selective screening for CKD in global health programs designed primarily to reduce CVD will significantly improve the outcomes of not only renal disease but especially the NCDs such as diabetes and CVD that dominate future health care strategies. Roadmaps for accomplishing

this have already been presented for both developed (39,40) and emerging (1,41) countries. However, effective implementation of such strategies will come only when both the general public and the renal community work together to convince health authorities that it is in the public interest to do this. It is our sincere hope that worldwide celebration of World Kidney Day 2011 will provide an opportunity to reinforce the message that kidney disease is indeed common, harmful, and treatable and that protecting your kidneys is an important health strategy that may save your heart.

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Disclosures

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