The Contribution of chronic kidney disease to the global burden of major noncommunicable diseases

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Noncommunicable diseases (NCDs) are the most common causes of premature death and morbidity and have a major impact on health-care costs, productivity, and growth. Cardiovascular disease, cancer, diabetes, and chronic respiratory disease have been prioritized in the Global NCD Action Plan endorsed by the World Health Assembly, because they share behavioral risk factors amenable to public-health action and represent a major portion of the global NCD burden. Chronic kidney disease (CKD) is a key determinant of the poor health outcomes of major NCDs. CKD is associated with an eight- to tenfold increase in cardiovascular mortality and is a risk multiplier in patients with diabetes and hypertension. Milder CKD (often due to diabetes and hypertension) affects 5–7% of the world population and is more common in developing countries and disadvantaged and minority populations. Early detection and treatment of CKD using readily available, inexpensive therapies can slow or prevent progression to end-stage renal disease (ESRD). Interventions targeting CKD, particularly to reduce urine protein excretion, are efficacious, cost-effective methods of improving cardiovascular and renal outcomes, especially when applied to high-risk groups. Integration of these approaches within NCD programs could minimize the need for renal replacement therapy. Early detection and treatment of CKD can be implemented at minimal cost and will reduce the burden of ESRD, improve outcomes of diabetes and cardiovascular disease (including hypertension), and substantially reduce morbidity and mortality from NCDs. Prevention of CKD should be considered in planning and implementation of national NCD policy in the developed and developing world.

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Noncommunicable diseases (NCDs) have replaced communicable diseases as the most common causes of morbidity and premature mortality worldwide.[1–3] An estimated 80% of the burden occurs in low- or middle-income countries, and 25% is in people younger than 60 years.[1] Moreover, the global economic impact of NCDs is enormous: by 2015, just two diseases (cardiovascular disease and diabetes) are expected to reduce global gross domestic product by 5%.[1] Approximately half of the total economic burden is accounted for by cardiovascular disease including stroke, ischemic heart disease, and peripheral vascular disease, which together cause more deaths than HIV/AIDS, malaria, and tuberculosis combined.[1,4] In recognition of the increasing burden and importance of chronic diseases, in 2008 the World Health Assembly endorsed a Global NCD Action Plan for NCD prevention and control.[5]

Four NCDs (cardiovascular disease, cancer, diabetes, and chronic respiratory disease) have been prioritized in the Global NCD Action Plan endorsed by the World Health Assembly in 2008 because they share major behavioral risk factors amenable to public-health action and together contribute to a major portion of the global NCD burden. Although not currently identified as a separate target, there is compelling evidence that kidney disease is a key determinant of the poor health outcomes of diabetes and cardiovascular disease (including hypertension), and prevention of kidney disease requires attention within national NCD programs particularly at the primary-care level as recommended by the WHO.[2,6]

CHRONIC KIDNEY DISEASE: THE GLOBAL PERSPECTIVE

Importance of chronic kidney disease

One potential outcome of chronic kidney disease (CKD) is end-stage renal disease (ESRD), requiring costly renal replacement therapy in the form of dialysis or transplantation. In developed countries, ESRD is a major cost driver for health-care systems, with annual growth of dialysis programs ranging between 6% and 12% over the past two decades and continuing to grow, particularly in developing countries. Although the incidence of ESRD shows signs of leveling off in developed countries, perhaps in part because of increased awareness of CKD, no such trend is seen in developing countries or minority populations. Over 2 million people now require renal replacement therapy to sustain life worldwide, but this likely represents less than 10% of those who need it.[6] In middle-income countries, access to these life-saving therapies has progressively increased over the same period. Efforts continue to reduce the cost of chronic dialysis, and to make kidney transplantation more widely available as the cost of immunosuppressive medications comes down; but nevertheless renal replacement therapy remains unaffordable for the majority of the affected and causes severe financial hardship for those who have access to it.[2] Another 112 countries, with a combined population of over 600 million people, cannot afford renal replacement at all—resulting in the death of over 1 million people annually from untreated kidney failure.[3,7] Motivated by the dismal outcomes and high costs associated with kidney failure, the past two decades have witnessed a marked increase in attention to the prevalence, prevention, and consequences of earlier and milder forms of renal impairment (CKD).

i. CKD is increasingly common in developed and developing nations. Kidney disease is conventionally assessed in terms of both overall renal function (glomerular filtration rate, GFR) and the presence of kidney damage ascertained by either kidney biopsy or other markers of kidney damage such as proteinuria (also termed albuminuria and defined by a urine albumin/creatinine ratio of >30 mg/g or urine protein/creatinine ratio >200 mg/g), abnormal urinary sediment, abnormalities on imaging studies, or the presence of a kidney transplant.[8] GFR is estimated in clinical practice using readily calculated equations that adjust serum creatinine values to age, sex, and ethnicity. It is important to recognize that both serum creatinine and albuminuria can be easily assessed using readily available, inexpensive laboratory testing.[6]

CKD is classified into stages 1–5, with stages 1 and 2 requiring the presence of kidney damage such as proteinuria as well as reduced GFR.[8] Many authors now refer to 'moderate,' or clinically significant, CKD as stages 3 (GFR 30–59 ml/min) and 4 (GFR 15–29 ml/min), with <60 ml/min chosen as a cutoff because it represents loss of about 50% of normal renal function, although there is now ample evidence of increased risk in earlier stages.[9,10] The role of proteinuria as well as GFR measurements in assessing risk of CKD is particularly important since people with stage 1–2 CKD and proteinuria have worse outcomes than people with stage 3 and no proteinuria, and development of both ESRD and cardiovascular disease is predicted much more accurately by proteinuria measurements than by GFR.[9,10] A recent meta-analysis of eight cohorts of 845,125 general and high-risk people confirms the marked and graded increased risk for ESRD in those with a GFR less than 60 ml/min (stage 3) and in people with albuminuria at all levels independent of traditional cardiovascular risk factors.[11] Stage 5 CKD is ESRD and is identified by GFR less than 15 ml/min or the need for dialysis.

This classification system has generated controversy regarding whether people identified as having CKD based primarily on estimated GFR measurements, particularly the elderly, actually have a 'disease.'[12] It has also required some modifications for different ethnic groups.[13,14] Newer schemes have been proposed to overcome many of the concerns about the Kidney Disease Outcomes Quality Initiative (KDOQI) classification.[15,16] Using a modification of the original GFR estimating equation (CKD-EPI equation), 11.6% of adult US residents have CKD stages 1–4 (approximately 26 million people), and the prevalence has increased over the past decade.[15] Of these, about 65% (7.5% of the total population) had moderate CKD (stage 3 or 4).[16] Similar figures have been reported from several other countries.[2,3,17,18]

According to the 2010 US Renal Data System Annual Data Report, the leading causes of CKD leading to kidney failure in the United States are diabetes (incident cases of ESRD of 153 per million population in 2009), hypertension (accounting for 99 per million population), and glomerulonephritis, which accounts for 23.7 per million population;[19] cardiovascular disease is also an important cause. However, in the United States about 28% of patients with clinically significant (stage 3 or worse) CKD are neither diabetic nor hypertensive, particularly those older than 65 years.[19,20] The proportion of people with CKD not explained by diabetes or hypertension is substantially higher in developing countries. In developing countries, diabetes and hypertension now appear to be the leading causes of ESRD with a prevalence of about 30% and 21%, respectively, but glomerulonephritis and CKD of unknown origin account for a larger fraction of the total, especially in younger patients. For example, in a recent study of people with CKD detected by International Society of Nephrology-sponsored screening programs in China, Mongolia, and Nepal, 43% of people with CKD did not have diabetes or hypertension.[21] The estimated prevalence of moderate CKD in developed countries is variable but is generally between 5% and 7% of the total adult population and consistently increases over time within countries.[2,3,7] Given projected increases in the prevalence of major risk factors for CKD (including diabetes, hypertension, and cardiovascular disease), the prevalence of CKD in developing countries is expected to dramatically increase over the next two decades. Other less recognized factors will contribute as well. For example, there is strong evidence that intrauterine events linked to poor nutrition alter prenatal programming and lead to low nephron number, which represents another substantial risk factor for CKD in later life.[22] This is relevant to global health given the emerging food crises worldwide.

Over 2 million people are being kept alive by renal replacement therapy worldwide, the majority of whom are treated in only five countries (US, Japan, Germany, Brazil, and Italy) that constitute only 12% of world population. Only 20% are treated in about 100 developing countries that make up over 50% of world population. This depicts a clear and direct association between gross domestic product and availability of renal replacement therapy.

ii. CKD is harmful and expensive. Although more than 2 million people already have ESRD, it is now established that (even in developed nations) only a small minority of people with CKD will develop kidney failure, partly because of the competing risk of cardiovascular mortality. For instance, data from the United States show that for every patient with ESRD, there are more than 200 with overt CKD (stage 3 or 4) and almost 5000 with covert disease (stage 1 or 2).[23] In stage 3, representing almost 40% of the CKD population, the number that will progress to ESRD is estimated at only about 0.15–0.2% per year over 10–25 years.[24–26] A much greater problem is the now well-documented eight- to ten-fold increase in cardiovascular disease mortality in CKD populations, thus strongly linking CKD to cardiovascular disease, one of the four major NCDs prioritized in the Global NCD Action Plan (see below).[24,25,27]

The most obvious societal effect of CKD is the enormous financial cost and loss of productivity associated with advanced kidney disease. For instance, many developed nations spend more than 2–3% of their annual health-care budget to provide treatment for ESRD, while the population with ESRD represents approximately 0.02–0.03% of the total population.[28] The economic burden associated with milder forms of CKD is huge: more than twice the total cost of ESRD. In the United States, monthly costs associated with managing CKD alone are $1250 per month, and more than $3000 per month if diabetes and heart failure are present.[19] Medicare expenditures on CKD patients in the United States exceeded $60 billion in 2007 versus $25 billion for ESRD and represented 27% of the total Medicare budget.[19] These figures illustrate the 'multiplier effect' of CKD on morbidity and mortality as well as cost.

Moreover, CKD is associated with extremely high morbidity and mortality even in its earlier stages.[29–33] In the extreme, mortality of ESRD patients is 10 to 100 times greater than in age-matched controls with normal kidney function. ESRD is associated with very low quality of life—an average patient would be willing to give up 10 years of life on dialysis in exchange for 4 years with normal kidney function. The high burden of ESRD and associated costs, related adverse outcomes, and decreased productivity make it a significant public-health problem worldwide. Similar associations between CKD, ESRD, and events predictive of later cardiovascular disease have also been well documented in children.[34–36]

This situation is even worse in most developing nations, where ESRD constitutes a 'death sentence,' as renal replacement therapy is often unavailable or unaffordable: nearly 1 million people die with ESRD each year in developing nations.[7] At the individual level, CKD affects all facets of health: physical (increased burden of cardiovascular disease morbidity and mortality) and social (low quality of life, decreased productivity and job losses, family pressures, and mental disorders).[37,38]

iii. CKD is treatable. In the past decades, ample evidence from clinical trials and meta-analyses has shown the efficacy of several management options for CKD to reduce risk of progression to ESRD and to lower cardiovascular risk.[39,40] These treatments are based on the control of its established modifiable risk factors. Control of hypertension is the single most effective intervention. Pooled analyses of many of these studies have consistently shown that the lower the blood pressure, the slower the progression of CKD.[41] Control of proteinuria with inhibitors of the renin–angiotensin system is highly effective for slowing the progression of diabetic and nondiabetic CKD. In, addition, lifestyle intervention (weight loss, smoking cessation), tight diabetes control, and treatment of other cardiovascular risk factors such as dyslipidemia are linked to lower rates of progression to ESRD, and associated with significant reduction in cardiovascular morbidity and mortality. These interventions are integrated with the WHO core package of essential NCD interventions for primary care.[6]

iv. CKD disproportionately affects the poor. In addition to the well-documented relationships linking poverty with hypertension, diabetes, and cardiovascular disease, low socioeconomic status is also associated with CKD. In the National Health and Nutrition Examination Surveys (NHANES), people with lower income were disproportionately afflicted with a higher burden of CKD risk factors.[42] Lower income and social deprivation are associated with microalbuminuria, macroalbuminuria, reduced GFR, progressive kidney function loss, ESRD, and (among those with ESRD) less access to renal transplantation in studies from multiple developed nations.[42–54] Within the developing world, similar associations between lower income and increased burden of CKD are also seen. More importantly, the overall burden of CKD is already greater in developing nations than in developed nations—and due to the epidemic of diabetes, hypertension, and cardiovascular disease in these low-income settings, further rapid growth will continue.[7,55] Sadly, CKD already disproportionately affects the poor and the socially disadvantaged—a situation that is also expected to worsen over the coming decades.[7,18]

v. Awareness of CKD is low. As with many NCDs, awareness of CKD is low, generally less than 20%, even at more advanced stages and in developed nations.[20] In the United States, fewer than 5% of people with an estimated GFR less than 60 ml/min per 1.73 m^2 and proteinuria as a marker of kidney damage were aware of having CKD.[20] In those with CKD stage 3, awareness was only 7.5%, and for stage 4, less than 50%.[20] Awareness rates among those with CKD stage 3 or 4 were higher if comorbid diagnoses of diabetes and hypertension were present, but even then they were quite low (20% and 12%, respectively). As an example, in a recent analysis of almost 500,000 people in Taiwan who took part in a standard medical screening program, 12% had CKD, and less than 4% of those with CKD were aware of their condition.[27] Awareness of CKD in developing nations is markedly lower, which probably serves as a barrier to accessing appropriate care even where available.[56]

vi. The presence of CKD dramatically increases the risk of adverse outcomes among people with other NCDs. The majority of patients with CKD have diabetes, hypertension, and/or cardiovascular disease[19]—driven by a reciprocal relationship among these four major chronic diseases. CKD strongly predisposes to hypertension and cardiovascular disease; diabetes, hypertension, and cardiovascular disease are all major causes of CKD; major risk factors for diabetes, hypertension, and cardiovascular disease (such as obesity and smoking) also cause or exacerbate CKD; and evidence-based treatments for slowing progression of CKD also reduce complications from diabetes, hypertension, and cardiovascular disease. Just as costs are highest among people with CKD superimposed on other chronic diseases, the presence of CKD (reduced estimated GFR or proteinuria) identifies the subset of people with diabetes, hypertension, or cardiovascular disease who are at the highest risk of adverse outcomes but are least likely to receive appropriate treatment. Therefore, where resources are limited, the presence of CKD could be used to identify people with diabetes, hypertension, and/or cardiovascular disease in whom intervention might be most beneficial and economically attractive.[1,6]

vii. CKD is also linked to acute kidney injury. CKD not only increases risk of both ESRD and cardiovascular disease but is also associated with a significant and often preventable increase in risk of acute (reversible) kidney injury (AKI), which markedly worsens outcomes.[57] Although studied mostly in hospitalized patients and in developed countries, the incidence of AKI is estimated at about 5–7% of all hospitalized patients, with the highest incidence in those with cardiovascular disease.[58] AKI with an increase in serum creatinine of $\leqslant 167\,\mu mol/l$ (2.0 mg/dl) is associated with a tenfold increase in mortality and threefold increase in cost of hospitalization—and 40-fold and sixfold increases in mortality and costs, respectively, if the rise is greater than $167\,\mu mol/l$.[58] In the United States alone the costs of AKI have been estimated at about $10 billion per year, or 40% of the costs of treating patients with ESRD.[58]

Even transient increases in serum creatinine of as little as $25\,\mu mol/l$ in patients with CKD increase both the rate of progression to ESRD and all-cause mortality in comparison with patients without CKD.[59]

Such transient episodes of AKI can occur with several cardiovascular and diabetes medications, nonsteroidal anti-inflammatory agents, and traditional medicines used in developing-country primary-care settings, emphasizing the importance of CKD detection and appropriate adjustments in management for optimal outcomes in major NCDs. With respect to CKD, increased risk of AKI ranges from 3.54-fold in patients with stage 3 CKD and proteinuria to 28.5-fold in patients with stage 4, and up to 28% of patients with no preexisting kidney disease who recover from AKI develop *de novo* CKD.[60] Not only is acute dialysis for AKI extremely expensive and associated with poor outcomes, but it is not available in many developing-country settings, resulting in death from treatable and reversible causes for many young people with AKI due to things like dehydration or complications of pregnancy.

viii. Summary. CKD is a significant public-health problem,[61] on the basis of the tremendous burden of death and disability that it causes, its inequitable distribution among the poor, and the existence of effective and affordable treatments that are not available to a large proportion of those affected. In the sections below we summarize the data, which support the linkage of CKD to diabetes, hypertension, and cardiovascular disease and thereby the rationale for considering prevention of CKD through early detection and treatment in national NCD policy agendas particularly at the primary-care level.[6]

CKD and diabetes

i. Diabetes is a major public-health problem. Over the past 25 years, the prevalence of type 2 diabetes has almost doubled in the United States and has increased three- to fivefold in India, Indonesia, China, Korea, and Thailand.[62,63] As with other NCDs, the increase in prevalence of diabetes will be most rapid in developing countries. According to the WHO, China and India will have about 130 million people with diabetes in 2025, and these people will consume about 40% of total health expenditures in the countries.[1] Indeed, 30% of the predicted $1.1 trillion global cost of dialysis during the current decade will result from diabetic nephropathy, now the most common cause of ESRD worldwide.[62,63] Despite this, only 8.7% of the general population was able to identify diabetes as a risk factor for kidney disease,[64] and among patients with diabetic kidney disease, very few are aware of their kidney condition.[62,65] The increasing prevalence of diabetes has been called, with some justification, 'a medical catastrophe of worldwide dimensions.'[65]

ii. Diabetes is a major cause of CKD. CKD is common in diabetes and is a major determinant of adverse outcomes. Over 5% of people with newly diagnosed type 2 diabetes already have CKD, and an estimated 40% of both type 1 and type 2 diabetics will develop CKD during their lifetimes—the majority within 10 years of diagnosis.[66,67] The prevalence of stage 3 or worse CKD in US diabetics exceeds 15%,[19,20] and CKD in diabetes carries an increased risk of progression to ESRD,[63] a death sentence in many parts of the world where dialysis is not available or affordable. About 45% of patients with ESRD in most developed countries have diabetes.[62,63] Reduced GFR and albuminuria caused by diabetic nephropathy are each major independent risk factors for both cardiovascular events and death.[68,69] In patients with ESRD due to diabetes, the prevalence of ischemic heart disease is increased 78%, and of congestive heart failure by 100%, over those in nondiabetic controls.[70] Although diabetic CKD is common, it is often unrecognized and untreated, especially in people with other NCDs: among people with diabetes and normal serum creatinine levels who undergo coronary interventions, 77% have CKD.[71]

iii. If recognized early, diabetic CKD can be effectively treated. However, the good news is that relatively simple and inexpensive approaches are now available to address diabetes and diabetic nephropathy. Such programs include opportunistic screening in primary health care settings, lifestyle changes, and cost-effective medical interventions that are now both doable and affordable.[6,72–75] Recently, strong scientific evidence shows that treatment of diabetic nephropathy reduces cardiovascular complications as well as renal failure. The UK Prospective Diabetes Study,[73,74] the Steno-2 Study,[75] and the ADVANCE trial[76] all demonstrate that tight control of blood glucose level and blood pressure (and lipids in Steno-2) significantly reduces the incidence and progression of diabetic kidney disease. In people with type 2 diabetes, inhibition of the renin–angiotensin–aldosterone system using an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker decreased progression from normoalbuminuria to microalbuminuria,[77] reduced progression from microalbuminuria to macroalbuminuria,[78] and slowed the development of ESRD.[79] Even in underprivileged minorities, simple measures of intervention reduce the burden of ESRD, as documented by evidence-based intervention programs in communities of Australian aboriginals.[80,81] Thus the use of an angiotensin-converting enzyme inhibitor targeted at proteinuria and independent of blood pressure is now standard therapy for patients with diabetic nephropathy in addition to glucose, lipid, and blood pressure control.[6]

There are several examples of demonstration projects that have implemented early detection and prevention in developing countries. In India, young women were trained to measure blood pressure and carry out simple urine tests, and the cheapest drugs, reserpine and hydrochlorothiazide, metformin, and glibenclamide, were administered.[82–85] Blood pressures lower than 140/90 mm Hg were achieved in 96% of people with hypertension, and a hemoglobin A1c level lower than 7% was achieved in 52% of people with diabetes[82] at an annual per capita cost of $0.27.[82] These encouraging findings indicate that simple and inexpensive strategies of early intervention are feasible and effective even in low-income settings.

CKD and cardiovascular disease

Hypertension. Raised blood pressure is a key NCD risk factor, and its prevalence, like those of diabetes and cardiovascular disease, is projected to increase sharply over the next few decades—especially in developing nations.[86] Nearly 1 billion people worldwide have high blood pressure (defined as $>140/90$ mm Hg). That number is higher if the currently recommended blood pressure goal of 130/80 is used, and it is expected to rise to 1.56 billion people by 2025, increasing by 24% in developed countries and by 80% in developing regions such as Africa and Latin America.[86] The prevalence of hypertension is highest in non-Hispanic blacks (53%) versus whites (43%) or Mexican Americans (34%). Moreover, hypertension, like diabetes and CKD, is more common in overweight or obese people (60% for body mass index $\geqslant 35$ versus 32% for body mass index of 23).[87] As with CKD, awareness of hypertension is low. Slightly more than half of US adults with hypertension were aware of their disease in 1999–2004; fewer than half were treated for their hypertension with medications; and fewer than two-thirds of those achieved good control.[8,19] This problem is worse in developing countries.[88] For low- and middle-income countries, the WHO recommends an absolute risk approach for cost-effectively lowering the cardiovascular risk of all people with raised blood pressure to prevent heart attacks, strokes, and renal disease.[80] A combination of population-wide and individual health-care interventions is required to make control of hypertension affordable and equitable in these lower income settings.[1,6,89–91]

i. CKD is a cause and consequence of hypertension. CKD is both a cause and a consequence of hypertension. Kidney dysfunction is a major cause of hypertension, and hypertension in turn aggravates CKD and accelerates its progression.[85] The presence of CKD is a common and underappreciated cause of resistant hypertension.[92] Hypertension is now the major risk factor for development and progression of diabetic and nondiabetic CKD.[86,93]

ii. Hypertension often coexists with and exacerbates CKD. The prevalence of hypertension is significantly higher (50–60%) in people with CKD than in the general population and rises to 90% in CKD patients aged more than 65 years.[19] In the United States, approximately 26% of people with hypertension have concomitant CKD.[16,19] In CKD screening studies in the general population, the presence of microalbuminuria has been shown to predict later development of hypertension.[94] The renal consequences of hypertension are uniquely exaggerated in the CKD population because a loss of the normal nocturnal decline in blood pressure ('dipping') usually occurs, which aggravates the severity of daytime elevations and is more closely associated with proteinuria than with GFR.[95] Other observations also suggest co-primacy of hypertension and CKD in the etiology of cardiovascular disease,[96] emphasizing the interrelated nature of these conditions.

iii. Control of hypertension is especially suboptimal when CKD is also present. Not only is the adverse renal and cardiovascular impact of hypertension increased in the setting of CKD, but the likelihood that hypertension will be appropriately controlled is substantially reduced when it coexists with CKD—especially when diabetes or proteinuria is also present.[86,87,97] In the US National Kidney Foundation's Kidney Early Evaluation Program (KEEP; a health-screening program for people at high risk for CKD), the prevalence (86%), awareness (80%), and treatment (70%) of hypertension in the screened cohort were high, but good blood control was achieved in only 13%.[97] NHANES data compiled by the US Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team also document significantly poorer blood pressure control in patients with CKD.[98]

iv. Opportunistic screening for CKD in people with hypertension may help to improve outcomes. Many studies document the beneficial effect of blood pressure control on renal as well as cardiovascular outcomes in both adults and children.[99-101] There is no direct evidence that screening for CKD will further improve outcomes in hypertensive patients as compared with simply measuring and treating blood pressure alone. However, indirect evidence suggests that screening for CKD in this population is beneficial. First, the treatment of hypertension may require modification or intensification in the setting of concomitant CKD,[86,98] suggesting that knowledge of a patient's CKD status would be clinically useful. For example, evidence-based management of hypertension in CKD should include inhibition of the renin–angiotensin system, and perhaps lower systolic blood pressure targets—especially if proteinuria is also present.[102,103] Second, data from the KEEP screening program demonstrate that blood pressure control is better among patients who are aware that they have CKD, as compared with those who are unaware[97]—perhaps because this knowledge motivates patients to adhere to appropriate care. This observation is supported by data from Bolivia indicating that physicians are more likely to manage hypertension appropriately once CKD is identified.[104]

Cardiovascular disease (excluding hypertension). i. Cardiovascular disease is a major public-health problem. Cardiovascular disease is the most common NCD—accounting for about 30% of all deaths worldwide and 10% of all healthy life lost to disease.[1,4] Well-established conventional risk factors for premature cardiovascular disease include tobacco use, physical inactivity, unhealthy diet, obesity, diabetes, hypertension, and hyperlipidemia as well as age and male gender.[1,105,106] Although mortality from cardiovascular disease has been declining in the general population in developed countries, no such decline is seen in developing countries, minority populations, or people with accompanying CKD.[19,31] Cardiovascular disease itself is a major risk factor for CKD[107,108] and is associated with substantial increases in the incidence of CKD (acute myocardial infarction, 33%; congestive heart failure, 46%).[107,108]

ii. CKD is a major independent risk factor for cardiovascular disease. It has long been appreciated that there is a 20- to 30-fold increase in cardiovascular disease in patients with ESRD. In 2004, it was definitely shown that even milder forms of CKD are associated with excess cardiovascular risk: a community-based study of over 1 million US adults noted an independent and graded association between GFR and risk of death, cardiovascular events, and hospitalizations.[9] Increased risk in patients with CKD has been demonstrated for angina, myocardial infarction, heart failure, stroke, peripheral vascular disease, arrhythmias, and sudden death.[30,31,109]

iii. Even mild reductions in GFR are associated with substantial increases in cardiovascular risk. More evidence that this increased cardiovascular risk is attributable to CKD and not solely to coexisting diabetes or hypertension has been provided in subsequent studies. For example, in a study of 6447 people followed for a mean period of 7 years, the risk of cardiac death was increased 46% in people with GFR between 30 and 60 ml/min (stage 3 CKD) independent of traditional cardiovascular risk factors including diabetes and hypertension.[110] The Cardiovascular Health Study of over 6000 US adults showed a risk for cardiovascular events and mortality in people over 55 with CKD alone that was equivalent to that in patients with diabetes or previous myocardial infarction.[111] In another study, the hazard ratio for cardiac death was actually higher in patients with CKD (relative risk 1.96) than in patients with diabetes (relative risk 1.49) or demonstrable myocardial perfusion defects (relative risk 1.90).[112] The increased risk of cardiovascular disease associated with CKD has been well documented in both general[19,112,113] and high-risk[113] populations. The excess risk is not confined to the elderly—in a study of 31,000 community volunteers with an average age of 45, the presence of CKD doubled the risk for myocardial infarction, stroke, and all-cause mortality.[114] Nor is the excess risk confined to white populations: CKD is an important risk factor for mortality among US[30] and African blacks,[115] as well as in people from Asia.[116] Reviewing ten community-based cohort studies in Japan and adjusting for diabetes and hypertension as risk factors, Ninomiya *et al.* reported a 57% greater risk of cardiovascular disease in patients with GFR less than 60 compared with those with GFR greater than 90 ml/min.[117]

iv. Albuminuria and proteinuria are also independently associated with excess cardiovascular risk. The risk of mortality is better correlated with proteinuria (albuminuria) than with GFR alone.[31,116,118,119] A large population-based study of more than 1 million people from Alberta, Canada, demonstrated that the presence of proteinuria was associated with marked increases in the risk of all-cause mortality and the risk of kidney failure, independent of GFR and at all levels of baseline kidney function.[29] Similar associations linking proteinuria to stroke, myocardial infarction, and coronary revascularization have also been reported.[120,121] Data from the US NHANES database confirm the increased risk of cardiovascular disease both with reduced GFR and with albuminuria and document the independent effect of albuminuria on risk of both cardiovascular disease and all-cause mortality at all levels of GFR; for example, the presence of microalbuminuria almost doubles the cardiovascular disease rate in patients with GFR of 16–59 (stage 3–4 CKD) and 60–89 ml/min (stage 2 CKD).[119] Although there has been concern that CKD identified by reduced GFR alone is found predominantly in older adults,[122] the association between proteinuria and cardiovascular mortality independent of hypertension, diabetes, and GFR has recently been demonstrated in a meta-analysis of 22 studies[30] including participants with a wide range of ages from around the world. The independent risk associated with proteinuria for all-cause mortality, cardiovascular mortality, and progression to ESRD was confirmed in over 1.1 million people with proteinuria identified only by detection of 'trace' or greater on dipstick urinalysis, as well as in over 100,000 who had an albumin/creatinine ratio (ACR) of 10 mg/g or more.[30] Similar findings were consistent in younger and older participants and are supported by a meta-analysis of ten cohorts of 266,975 people at increased risk of CKD that demonstrated increased risk for both cardiovascular disease and all-cause mortality with both reduced GFR and increased albuminuria independently of each other.[123]

These findings have also been confirmed in a broad range of ethnic populations. For example, in a study of 96,736 Japanese adults 40–79 years old followed for 10 years, Irie *et al.* confirmed the independent and additive effects of both proteinuria and reduced GFR on the risk of cardiovascular death.[124] The prognostic importance of proteinuria is also observed in people with cardiovascular disease. For example, in survivors of myocardial infarction, proteinuria was associated with a higher risk of death than reduced GFR.[125] Similar findings were reported in patients with congestive heart failure but without diabetes, hypertension, or reduced GFR, in whom increased albuminuria was strongly associated with both cardiovascular and all-cause mortality.[126] Another study indicates that not only did the likelihood of cardiovascular events increase, but the time to development of a cardiovascular event is significantly and independently reduced in the presence of proteinuria at all levels of GFR.[127]

Most of these studies have quantified proteinuria using laboratory-determined albumin/creatinine or protein/creatinine ratios. However, semiquantitative, point-of-care measures of proteinuria that do not require a laboratory are also effective for risk stratification at all levels of baseline GFR.[29,120,128,129] In a large community-based study of 1,120,295 adults, Go *et al.* showed that the presence of 1 + or greater proteinuria identified by dipstick urine testing increased the risk of developing cardiovascular disease by 30%, independent of baseline GFR.[9]

A recent paper examined the contribution of eGFR and ACR independent of traditional risk factors to the prediction of risk for cardiovascular and renal outcomes, using a sample of people with established cardiovascular disease who participated in two clinical trials.[130] The data again showed that GFR and ACR were important independent predictors of progressive renal function loss. Although the authors also found that the renal parameters added little for prediction of cardiovascular risk, their analysis used a very restrictive definition of risk classification based on arbitrary risk categories and focused on people who already had cardiovascular disease. Since this study included a limited number of people with heavy proteinuria, its conclusions may not be generalizable to the broader population with CKD. For example, recent data from the Uppsala Longitudinal Study of Adult Men study in 1113 older men indicate that both GFR and albuminuria did improve cardiovascular disease risk prediction beyond traditional cardiovascular risk factors in the population that did not have prevalent cardiovascular disease.[131]

The excess risk associated with albuminuria extends to very low levels that were considered innocuous until recently (15–29 mg/d). A population-based study from the Netherlands demonstrated an exponential relationship between albuminuria and the risk of cardiovascular death—with a nearly 50% increase in risk observed for albuminuria of 15–29 mg/d, as compared with albuminuria less than 15 mg/d. In contrast, the risk was increased sixfold among people with albuminuria exceeding 300 mg/d.[118] The Third Copenhagen Heart Study confirmed an increased risk of coronary disease and mortality at very low levels of albumin excretion independent of other risk factors including hypertension and diabetes.[132] Such levels of albuminuria are also independently associated with increases in left ventricular mass, an established predictor of subsequent cardiovascular events.[133] Moreover, subdividing stage 3 CKD according to the presence or absence of a urinary albumin excretion rate greater than 30 mg/d improves cardiovascular risk stratification, further indicating the predictor value of albuminuria.[134]

Further emphasizing the independent nature of albuminuria as an independent risk factor, a positive association between albuminuria and all-cause mortality was found in nondiabetic, nonhypertensive people after a 4.4-year follow-up.[135] An ACR greater than 6.7 μg/mg in three urine samples increased the risk for all-cause mortality 2.4-fold. Subjects with an ACR greater than or equal to the sex-specific median (>3.9 mg/g for men, >7.5 mg/g for women) experienced a nearly threefold increased risk of cardiovascular disease (adjusted hazard ratio 2.92, $P<0.001$) and a borderline-significantly increased risk of death (adjusted hazard ratio 1.75, $P=0.08$) compared with those with an ACR below the median.[136] Among people without hypertension or diabetes, baseline presence of albuminuria predicted development of blood pressure incrementally over established risk factors and at levels well below the conventional threshold for microalbuminuria.[137]

Thus, multiple studies confirm that proteinuria (a parameter that has been included by the WHO as an essential diagnostic test for primary care[6]) is in fact a graded risk factor for cardiovascular disease independent of GFR, hypertension, diabetes, and traditional cardiovascular risk factors and that this risk extends down into ranges of albumin excretion generally considered normal.[118,134,138–143]

v. Identification and treatment of CKD may also reduce cardiovascular risk. Interventions designed specifically to reduce proteinuria and slow progression of CKD also effectively reduce cardiovascular risk. The benefits of therapy with an angiotensin-converting enzyme inhibitor (ACEI) for slowing progression of established diabetic and nondiabetic CKD are well established.[99,100,144,145] Recent data indicate that, independent of other risk factors (including baseline GFR), more rapid loss of kidney function is strongly associated with the risk of coronary events, suggesting that interventions that prevent kidney function loss may also prevent cardiovascular events.[146] Another analysis in people with type 2 diabetes showed that the risk of cardiovascular outcomes was significantly reduced in proportion to the reduction of albuminuria with ACEI therapy; e reduction in albuminuria was associated with an 18% reduction in cardiovascular risk, and albuminuria was the only predictor of cardiovascular outcome.[147] Other studies also show that changes in proteinuria are more predictive of outcomes than the change in blood pressure achieved with ACEI therapy.[148] These findings suggest that treatments targeting proteinuria specifically (such as higher doses of renin-angiotensin system blockers than are required for blood pressure control) may further improve clinical outcomes, independent of their effects on blood pressure or GFR.[149]

A pilot randomized controlled trial that identified people from the general population who had albuminuria and randomized them to receive an ACEI versus placebo found a trend toward reduction in cardiovascular events over 4 years even in people with no other risk factors.[147] In this study, treatment was most effective (and likely to be cost-effective) in people with albumin excretion greater than 50 mg/d.[150] The Heart Outcomes Prevention Evaluation (HOPE) study also reported a decrease in cardiovascular mortality in high-risk people with CKD (reduced GFR) who were treated with ACEIs;[89] the relative benefit in this population was similar to the benefit in people without CKD, but the absolute benefit was greater in those with CKD because of the higher baseline risk. Combination, multimodal therapy of people with reduced GFR and/or albuminuria (using blood pressure control, ACEIs/angiotensin receptor blockers, sodium restriction, statins, and aspirin) was associated with highly favorable cardiovascular outcomes and stability of kidney function.[151] These data indicate that treatment of CKD as defined by either low GFR or albuminuria will improve health by delaying or preventing cardiovascular disease.

Summary

CKD is an important public-health problem that is closely linked to other major NCDs such as diabetes and cardiovascular disease (including hypertension)—but which independently increases the likelihood of adverse outcomes and high health-care costs, suggesting that it can be used to identify the highest risk subset of patients, who may benefit most from treatment. Further, optimal management of these other NCDs may require modification when CKD is also present.

THE RATIONALE FOR EARLY DETECTION OF CKD THROUGH A PRIMARY HEALTH CARE APPROACH

i. Measuring albuminuria and GFR in populations at risk for NCDs would meaningfully enhance risk prediction. Laboratory measurements of albuminuria and serum creatinine (to estimate GFR) are potentially useful additions to assessment of cardiovascular risk in primary-care settings. Measurement of urine albumin is already recommended for cardiovascular risk assessment in primary care even in resource-constrained settings.[6] Measurement of serum creatinine in selected patient groups is also recommended but is not feasible in primary-care settings at present in most low-income countries. The importance of considering proteinuria and reduced GFR separately is illustrated by the fact that in the United States only 25% of people with proteinuria have reduced GFR and only 25% of those with a low GFR have proteinuria[152]—and thus, focusing on either alone would miss a substantial proportion of people at risk. Albuminuria has been shown to predict the development of both hypertension[94,137] and diabetic nephropathy.[74] Finally, increases in albumin excretion can precede elevations in both blood sugar and blood pressure—thus identifying a population of patients that would not be detected by conventional screening methods for diabetes or hypertension.[137]

ii. Measuring albuminuria in populations at risk for NCDs is practical and inexpensive. Readily available, inexpensive measurements of proteinuria using dipstick urinalysis alone are sufficient to identify high-risk patients.[9,125,138] Albumin dipsticks have a sensitivity of 88%, specificity of 80%, positive predictive value of 89%, and negative predictive value of 92% for detection of albuminuria—adequate for screening in most point-of-care settings.[138] More sophisticated measurements such as albumin/creatinine or protein/creatinine ratio are more sensitive for detection of less severe proteinuria but are more expensive and can be less easy to use at the point of care.[153]

CKD can be identified opportunistically during health-care encounters for management of other NCDs. For example, among nondiabetic subjects with normal serum creatinine levels undergoing percutaneous coronary interventions, about 78% had demonstrable CKD when screened more stringently for renal function (GFR, urine protein); 17% of those older than 65 years and 5% of those younger than 65 years had stage 3 or worse CKD.[154] The presence of CKD likely accelerated the development of coronary disease in these patients but also appears to increase their risk of periprocedural hemorrhage, contrast nephropathy, restenosis, and death.[155] CKD can also be identified in economically disadvantaged settings by mobile clinics and point-of-care laboratory testing. For example, a recent study from Mexico found that more than 30% of people with no history of cardiovascular disease who agreed to be screened for CKD and other cardiovascular risk factors had a projected risk of 30% for a cardiovascular event in the next 5 years.[127] A further 27% of these people had CKD that had not been previously recognized.

A recent high-quality economic analysis showed that using GFR to screen people from the general population with diabetes for CKD was highly cost-effective, independent of age.[129] Previous studies have reached similar conclusions about the benefits of screening using dipstick urinalysis or protein/creatinine ratio in people with diabetes, as well as the cost-effectiveness of treatments directed at reducing proteinuria in the subset of this population who are found to have CKD.[156] No direct evidence currently demonstrates the effectiveness and cost-effectiveness of screening for CKD in nondiabetic people without additional CKD risk factors.[157] However, because identification of CKD is expected to change management and improve outcomes (see below), screening for CKD in nondiabetic patients older than 55 years is currently recommended.[33,158]

iii. Identification of CKD would change management of NCDs and improve outcomes. The rationale for including the prevention (or the slowing of the progression) of kidney disease in the public-health agenda for NCDs is usually provided by promises to reduce the enormous cost of renal replacement therapy. However, the substantial impact of CKD on cardiovascular disease and increases in costs associated with CKD itself provide a much more compelling rationale for including screening for CKD in government health programs, especially in high-risk populations. One example is the need to alter management of patients with CKD to minimize the increased risk of AKI mentioned above.

iv. Early detection of CKD in developed countries. A recent expert panel has made recommendations to the US Centers for Disease Control and Prevention on how to accomplish this.[159] The implementation of mandatory calculation of GFR whenever serum creatinine is measured in countries such as the United States and the United Kingdom, accompanied by information to providers on how to interpret these values, has led to significant increases in both awareness and detection of CKD. A number of entities now collect and report data on CKD in the population, including surveillance systems such as the US Renal Data System,[160] the National Health and Nutrition Examination Survey (NHANES),[161] the regional ESRD Networks,[162] and the Quality Improvement Organization system.[159] Similar renal registries now exist in most developed countries. In the United States, the National Kidney Foundation's Kidney Early Evaluation Program (KEEP) carries out systematic screening and kidney disease education in high-risk groups.[163] Several awareness programs are sponsored by the National Institutes of Health through the National Kidney Disease Education Program.[164] The US Centers for Disease Control and Prevention through their Chronic Kidney Disease Initiative are undertaking CKD surveillance programs and an economic impact study designed to meet national Healthy People 2010 objectives and have developed new diagnostic codes for CKD.[165] The United Kingdom has recommended increased attention to early screening for CKD and added CKD screening as part of primary-care doctors' chronic-disease assessment incentive payments. In 2000, the National Kidney Foundation of Singapore initiated a comprehensive program that has screened more than 450,000 people and has already reduced the risk of progressive CKD and related NCDs among Singaporeans.[166] Effective programs aimed at preventing, identifying, and treating CKD have led to substantial reductions in the incidence of ESRD in Japan and promising improvements in the prevalence of CKD in Australia and Taiwan.[17,167]

v. Health systems of developing countries are already scaling up efforts to identify and treat CKD. In the developing world the challenges are considerably greater.[1,2,7] However, significant progress is being made. The Kidney Disease: Improving Global Outcomes (KDIGO) group continues to develop evidence-based approaches to providing care to kidney patients.[168,169] The International Society of Nephrology (ISN), through its Global Outreach Research and Prevention Committee, has focused on demonstrating that early detection and prevention programs can be carried out cost-effectively in very resource-poor settings using the Chronic Kidney Disease, Hypertension, Diabetes and Cardiovascular Disease (KHDC) template.[170,171] KHDC projects have now been supported and implemented at a research level in 22 settings in 15 countries, and data from over 60,000 screened people undergoing longitudinal follow-up are being collected and analyzed at the Kidney Disease Data Center at the Mario Negri Research Institute in Bergamo, Italy.[172] This ISN program has also assumed responsibility for collecting and analyzing data on renal and urologic diseases for the WHO Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2005 Study), which is now ongoing.[171] A recent survey by the International Federation of Kidney Foundations evaluated CKD screening programs in 28 countries (most in the developing world) and showed significant improvement in program performance between 2005 and 2007, with continued growth expected.[173] National health systems in some developing countries, such as Uruguay, have already incorporated CKD into their NCD prevention and control programs. Mexico has recently launched the Strategic Network of Health Services against Chronic Kidney Disease. However, before such efforts are expanded on a national scale, it is necessary to obtain more information on sustainability, opportunity costs, and affordability of such programs to the public sector of low- and middle-income countries.

vi. Efforts to raise awareness about CKD. Important as all of these surveillance and data-gathering programs are, the resources to implement effective early detection and prevention programs for CKD (like all NCDs) must ultimately come from government health programs to improve the public health, to decrease the costs of managing CKD and cardiovascular disease, and to respond to public demand. World Kidney Day is a joint initiative of ISN and the International Federation of Kidney Foundations, which is organized to raise awareness regarding CKD. The sixth World Kidney Day (2011) focused on the kidney and cardiovascular disease and was celebrated with events in over 100 countries that included public activities such as free screenings for CKD and also meetings between leaders in the renal community and high-level government officials (including health ministers, prime ministers, and even presidents).[63] Over the next few years, continued growth of World Kidney Day is expected, allowing its associated activities to be progressively more effective for increasing awareness of CKD (and the other NCDs that often accompany CKD, such as diabetes, hypertension, and cardiovascular disease) among the general public as well as government decision makers.

SUMMARY AND ACTION PLAN FOR THE FUTURE

Top priority for prevention of all NCDs (including CKD) must focus on effective and cost-effective methods to control tobacco use, reduce harmful use of alcohol, facilitate physical activity, and promote a healthy diet (including salt reduction in processed food). In addition, individual disease-specific health-care interventions are also required to address those with disease or at high risk of developing disease. Ironically, some government programs that reimburse the enormous cost of renal replacement therapy often provide little or no incentive to conduct inexpensive early detection and prevention programs that have the potential to reduce those costs in the future. There is strong evidence supporting the detection and treatment of CKD as a key component of integrated national NCD strategies.[39] The major benefits will occur in people at high risk and in developing countries. Simple and inexpensive measurements of proteinuria (and, if affordable, GFR) can be used for case finding, especially in high-risk populations, including people over 55 and those with diabetes, hypertension, cardiovascular disease, and a family history of kidney disease. These recommendations are already incorporated in the WHO package of essential NCD interventions for primary care and have been incorporated into government policies in several developed countries, including the United States, the United Kingdom, Japan, Australia, and Canada. Further efforts to implement the inexpensive, cost-effective interventions now available to treat people found to have CKD (including reduction in proteinuria, and control of traditional cardiovascular risk factors) must be extended to other countries—especially in the developing world, where the burden of NCDs is especially high. Such interventions will reduce the risk of both ESRD and cardiovascular disease—and thereby improve health outcomes to the maximum extent possible.

DISCLOSURE

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