Traditional and emerging cardiovascular and renal risk factors: An epidemiologic perspective

C Zoccali[1]

[1]Division of Nephrology, Hypertension and Renal Transplantation, CNR Centro di Fisiologia Clinica, Reggio Calabria, Italy

Patients with chronic kidney disease (CKD) represent an important segment of the population (7–10%) and, mostly because of the high risk of cardiovascular complications associated with renal insufficiency, detection and treatment of CKD is now a public health priority. Traditional risk factors can incite renal dysfunction and cardiovascular damage as well. As renal function deteriorates, non-traditional risk factors play an increasing role both in glomerular filtration rate (GFR) loss and cardiovascular damage. Secondary analyses of controlled clinical trials suggest that inflammation may be a modifiable risk factor both for cardiac ischemia and renal disease progression in patients with or at risk of coronary heart disease. Homocysteine predicts renal function loss in the general population and cardiovascular events in end-stage renal disease (ESRD), but evidence that this sulfur amino acid is directly implicated in the progression of renal disease and in the high cardiovascular mortality of uremic patients is still lacking. High sympathetic activity and raised plasma concentration of asymmetric dimethylarginine (ADMA) have been associated to reduced GFR in patients with CKD and to cardiovascular complications in those with ESRD but again we still lack clinical trials targeting these risk factors. Presently, the clinical management of CKD patients remains largely unsatisfactory because only a minority of these attain the treatment goals recommended by current guidelines. Thus, in addition to research into new and established risk factors, it is important that nephrologists make the best use of knowledge already available to optimize the follow-up of these patients.

Kidney International (2006) **70,** 26–33. doi:10.1038/sj.ki.5000417; published online 24 May 2006

KEYWORDS: cardiovascular risk; CKD; ESRD; uremia; emerging risk factors; traditional risk factors

Correspondence: *C Zoccali, CNR IBIM Epidemiologia Clinica delle Malattie Renali e dellIpertensione Arteriosa e Unita Operativa, Via vallone Petrara, Reggio Cal 89124, Italy. E-mail: carmine.zoccali@ibim.cnr.it*

Received 31 October 2005; revised 16 December 2005; accepted 17 January 2006; published online 24 May 2006

Nephrology has long been considered a niche specialty. Renal physicians are perceived as experts in relatively unusual immunologic diseases (such as lupus) and rare or orphan diseases. Even end-stage renal disease (ESRD), an often-used measure for quantifying the burden of chronic renal disease, is a rare condition affecting only one individual/1000 in the general population. In contrast, the heart failure syndrome alone has a prevalence of about 20/1000 in the general population. During the last 10 years or so, however, considerable evidence has accrued that mild-to-moderate degrees of renal insufficiency are much more frequent at the population level. Even more important, modest degrees of renal dysfunction imply a high cardiovascular risk. In this review, I will summarize the epidemiologic knowledge about the frequency of renal insufficiency both at the population level and in specific disease states, on cardiovascular risk in patients with varying degrees of renal insufficiency, on risk factors for renal disease progression and cardiovascular complications, and I will conclude with a brief overview on preventive strategies. Rather than providing an exhaustive assessment of risk factors peculiar to chronic kidney disease (CKD), like anemia, hyperphosphatemia, and vascular calcification, that are well covered in recent systematic and narrative reviews (see below), the principal scope of this appraisal is that of emphasizing the role of traditional risk factors and of updating knowledge on selected emerging risk factors.

RENAL INSUFFICIENCY: AN EPIDEMIOLOGIC OVERVIEW

Since much of the issues discussed in this review pertain to the risk of disease (be it renal or cardiovascular), it is useful to review the concept of 'risk factor' as formulated by Kannel almost 30 years ago.[1] Risk factors are markers that are statistically, but not necessarily causally, related to subsequent morbid events. The identification of causal risk factors, for example, smoking, has critical importance because it can allow interventions aimed directly at reducing or eliminating the deleterious factor in question. Non-causal risk factors (disease markers, e.g., serum creatinine) are useful in monitoring the evolution of a given disease and for prognostic purposes. Risk factors also include structural surrogates of impending cardiovascular events, for example, atherosclerosis as detected by echo-Doppler techniques or left-ventricular hypertrophy (LVH) detected by electrocar-

diogram or cardiac echography. These structural surrogates of subsequent cardiovascular events reflect the pathophysiologic processes that lead to heart failure, myocardial infarction, etc. The dimension of time is fundamental for correct interpretation of the association between a purported risk factor and a given event. Indeed, cross-sectional studies (surveys) are generally far more prone to bias than are prospective (cohort) studies. As the link between risk factors and clinical outcomes varies in different populations and disease states, validation of prognostic factors demands that they be specifically tested in the particular population in which they will be applied. This concept is particularly true in ESRD, where 'reverse causality' is pervasive.

Knowledge of the frequency of renal insufficiency at the community level remains limited. In fact, the only solid databases providing such information in samples representative of the American population are those of the III and IV National Health and Nutrition Examinations Surveys (NHANES). In these surveys, a moderate degree of renal impairment (glomerular filtration rate (GFR) 15–59 ml/min/1.73 m^2, as estimated by the Modification of Diet in Renal Disease (MDRD) formula) had a 4.2 and 3.7% prevalence, respectively.[2] Diabetes mellitus and age were strongly associated with renal insufficiency because the risk was 2.8 (NHANES II) and 4.9 (NHANES III) times higher in diabetic than in non-diabetic subjects and 10 times higher in subjects older than 60 years than in younger subjects.[3] This strong age dependence of renal insufficiency also emerged in an analysis based on a community-derived sample from the Framingham Offspring study, a survey that identified older age treatment for hypertension and diabetes as important correlates of high serum creatinine levels.[4] These observations were subsequently confirmed in longitudinal analyses of the same database.[5] Smoking, low high-density lipoprotein cholesterol, and mild renal insufficiency at baseline represented additional independent predictors of further renal function deterioration. Comparable information from outside the USA is scarce. In the AusDiab study, the prevalence of moderate renal failure (GFR <60, >30 ml/min/m^2) as assessed by the Cockcroft–Gault method was even more alarming, reaching 11%.[6] In the framework of an exemplary initiative aimed at generating epidemiological knowledge on renal dysfunction at population level in Groningen, the PREVEND study,[7] the incidence rate of moderate renal insufficiency was 4.2% in 4 years.[8] In the Framingham Offspring study, the incidence of moderate CKD was 9.4% in 18.5 years[5] and in the Atherosclerosis Risk in Communities study it was 7% in 9 years.[9] Thus, both in the USA and in Europe CKD is more frequent than previously thought.

The diabetic and hypertensive populations, elderly individuals, and those who chronically use anti-inflammatory agents are prototypical high-risk populations for renal insufficiency.[10] In the NHANES I and II cohorts, mild renal insufficiency developed at a rate of 7.7% per year in patients with hypertension.[11] In a small cohort of Spanish patients attending a hypertension clinic,[12] moderate renal insufficiency developed in 14% of patients over 13 years of follow-up. In the last decade, the high frequency of renal impairment as an epiphenomenon of cardiovascular damage and/or cardiac dysfunction has been fully recognized. In US Medicare patients admitted to the hospital with myocardial infarction or heart failure, the prevalence of moderate renal failure (creatinine clearance <60 ml/min/1.73 m^2) was very high, 60 and 52%, respectively, and these patients had a high risk of renal disease progression.[13] Similar observations also were made in a well-organized heart failure clinic in Canada[14] and in a recent analysis of the Digitalis Intervention Group trial,[15] a study that investigated the efficacy of digoxin among stable outpatients with moderate-to-severe heart failure.

CARDIOVASCULAR RISK IN PATIENTS WITH RENAL INSUFFICIENCY

Incident cardiovascular events both in community-based studies (that is, in unselected populations) and in selected populations with established cardiovascular disease are strongly associated with the level of renal function. In the Framingham Heart study,[16] the first community study looking into this problem, the association was evident but restricted only to male gender. In the Atherosclerosis Risk in Communities study, middle-aged men and women with moderate renal insufficiency had a 38% excess risk for incident atherosclerotic complications compared to subjects with normal renal function.[17] No excess risk was found in subjects with renal insufficiency in the NHANES I.[18] However, a well-defined risk excess emerged in an analysis performed in NHANES II.[19] A pooled analysis of four community-based studies (including the Framingham Heart study and the Atherosclerosis Risk in Communities study) showed that moderate renal insufficiency carries a 19% excess risk for cardiovascular complications.[20] Renal insufficiency signals a very high-risk situation, particularly in patients with pre-existing cardiovascular disease. In patients with essential hypertension, the relationship between serum creatinine concentration and cardiovascular risk is evident even within the boundaries of the normal range of serum creatinine. In an Italian cohort of about 2000 hypertensive patients with 'normal' serum creatinine levels (that is <1.5 mg/dl in men and <1.4 mg/dl in women) a 0.23 mg/dl higher serum creatinine was associated with a 30% higher risk for incident cardiovascular events.[21] Data from the Syst–Eur trial showed that in the elderly, a 10 ml lower GFR was associated with 5% excess risk for *de novo* cardiovascular complications.[22] In the 14,527 patients with myocardial infarction enrolled in the Valiant study, a 10 ml lower GFR signaled a 10% increase in risk of death or incident cardiovascular events, independently of whether patients were treated with valsartan, captopril, or both drugs.[23] In patients with heart failure, even small reductions in the GFR carried an important excess risk for death both in a Canadian heart failure clinic study[15] and in the Digitalis Intervention Group trial.[16]

Only a tiny minority of patients (about 1%) with mild-to-moderate renal insufficiency developed ESRD over a 5-year

follow-up in a retrospective cohort study by the Kaiser Permanente Center.[24] However, as many as 19 and 24% of patients with mild and moderate renal insufficiency respectively died, mostly because of atherosclerotic complications, during the same 5 years. Thus, the true risk of renal insufficiency is cardiovascular rather renal. Cardiovascular risk in patients who reach the end-stage phase of renal disease is staggering, being five times higher than normal in 85–95-year-old ESRD patients, and 65 and 500 times higher than normal in those 45–54 years old and 25–35 years old, respectively.[25]

THE CRUCIAL CARDIORENAL CONNECTION

There is a blossoming of studies describing new cardiovascular risk factors. New factors are being added almost daily to an already long catalogue including hundreds of such factors. As much as the 75% of excess risk for coronary heart disease in the general population could be explained by classical, Framingham risk factors.[26] The dominance of traditional risk factors in ischemic heart disease recently has been reaffirmed by the Interheart study,[27] a case–control examination of acute myocardial infarction in 52 countries, which included 15,152 patients and 14,820 controls, that analyzed the relation of smoking, hypertension, diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors to myocardial infarction. The risk attributable to dyslipidemia (raised apolipoproteins B/apolipoproteins A1) was the highest among the factors considered in this analysis (49.2%). Smoking (35.7%), hypertension (17.9%), diabetes (9.9%), abdominal obesity (20.1%), psychosocial factors (32.5%), lack of consumption of fruits and vegetables (13.7%), lack of regular alcohol consumption (6.7%), and of regular physical activity (12.2%) all were significantly related to acute myocardial infarction. These associations were noted in men and women, old and young, and in all regions of the world. Remarkably, the collective contribution of these nine risk factors accounted for 90 and 94% of the population's attributable risk in men and women, respectively. This study suggests that approaches to prevention of cardiovascular disease can be based on similar principles worldwide and have the potential to prevent most premature cases of myocardial infarction. Although not considered in the Interheart study, loss of renal function is an important element in the natural history of cardiovascular diseases, and it brings into the scene the importance of novel cardiovascular risk factors.

As I mentioned, cardiovascular risk increases as renal function deteriorates. It can be estimated that the (fully adjusted) risk associated with moderate renal insufficiency is about 40% higher than normal.[24] The risk increases linearly as renal function deteriorates until the GFR <15 ml/min. Thereafter, the relationship must be exponential because in ESRD patients, the cardiovascular death rate is 5–500 times higher than normal.[25] Thus, chronic renal insufficiency is a strong 'risk amplifier'. A possible explanation for why renal function is so closely associated with cardiovascular risk is that it simply constitutes a biologic marker of the severity of undetected and/or detected cardiovascular disease, or a measure of residual confounding from Framingham risk factors; that is, renal dysfunction might be the expression of a longer exposure to hypertension and/or to dyslipidemia. However, risk modeling studies suggest that it is unlikely that the excess risk for patients with chronic renal insufficiency can be explained only on the basis of traditional risk factors.[28,29]

In recent years, substantial progress has been made in identifying risk factors specific to patients with uremia. The huge risk excess associated with renal insufficiency might depend in part on the fact that renal dysfunction produces a positive sodium balance. The resulting extracellular volume expansion imposes a chronic volume and pressure burden on the left ventricle, ultimately producing left-ventricular remodeling and heart failure. Anemia, high calcium–phosphate product, inflammation, hyperhomocysteinemia, and impaired nitric oxide (NO) synthesis, due to accumulation of NO synthase inhibitors, all might contribute to the increase in cardiovascular risk in patients with ESRD.[29] Most of these factors affect generation of reactive oxygen species. High oxidative stress mediates the adverse effects of a multitude of risk factors on the ardiovascular system.[30] Yet no prospective study in CKD has provided convincing proof of such a link. Genetic factors, such as gene polymorphisms that regulate homocysteine levels, the renin–angiotensin system, and the endogenous antioxidant system itself, also are important. Furthermore, an absolute or relative deficiency in endogenous vasoprotectors such as adiponectin[31] might contribute to vascular damage.

Classical risk factors dominate the scene in the early stages of chronic renal insufficiency because most individuals who develop renal dysfunction have a long history of hypertension, diabetes, dyslipidemia, smoking, or a combination of these. Within the kidney, afferent vasoconstriction plays a key role in protecting the glomerular tuft from systemic pressure. In hypertensive patients, the afferent arteriole shows muscular hypertrophy and hyaline transformation, which lead to glomerular ischemia and tubulo-interstitial changes.[32] Males and smokers have an increased risk of these changes. Moreover, dyslipidemia is harmful both to the vascular system and to the kidney, and Diamond[33] has suggested that focal glomerulosclerosis is the glomerular equivalent of atherosclerosis. Diabetic nephropathy causes specific glomerular alterations and, nephrosclerosis is common in patients with diabetes mellitus.[34]

Traditional risk factors are considered dominant for triggering initial renal damage and cardiovascular events in the general population, but non-traditional risk factors – anemia and other emerging risk factors discussed below – become increasingly important as renal function worsens.

Anemia

The first signs of anemia become evident when GFR falls below 50 ml/min; on average, hemoglobin concentration is

2.5 g/dl lower in patients with GFR 50–25 ml/min than in those with GFR >50 ml/min, and a 0.5/dl decrease in hemoglobin concentration is associated with a 1.3-fold increased incidence of LVH.[35] However, it is unknown whether early treatment of anemia in patients with renal chronic renal insufficiency prevents LVH in these patients. Initial studies in animal models suggested that a higher hematocrit may accelerate renal function loss in the rat. However, observations in humans indicate that better control of anemia is unlikely to have detrimental effects on the progression of renal insufficiency.[36] Treatment of anemia might improve symptoms of heart failure[37] but there is no solid evidence that correction of anemia in heart failure affects the high death rate of this condition. Furthermore, it remains still to be proven that anemia increases life expectancy in patients with ESRD.[38]

Hyperphosphatemia and hyperparathyroidism

These constitute the second cardiovascular risk factor commonly seen in patients with chronic renal insufficiency. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR dependent and associated with cardiovascular disease. Indeed hyperparathyroidism is associated with a history of myocardial infarction and heart failure.[39] A strong association has been described between hyperphosphatemia and incident cardiovascular events in ESRD patients. Although further studies based on hard end points are still required, the link between hyperparathyroidism–hyperphosphatemia and cardiovascular complications probably is a causal one because vascular calcifications do not progress in patients with better control of hyperphosphatemia and hypercalcemia, while vascular calcifications worsen in patients with poor control of the plasma concentration of these substances.[40] The pathogenesis of cardiovascular calcifications is presently one of the most investigated in nephrology[41] and evidence is emerging that optimizing treatment of calcium and phosphate alterations may decrease cardiovascular risk in patients with CKD.[42]

Hyperhomocysteinemia

Hyperhomocysteinemia might trigger renal damage. In the Horn study, high plasma homocysteine was associated with microalbuminuria independently of other risk factors.[43] In a community-based study in individuals without renal disease at baseline, the risk of moderate-to-severe renal insufficiency (GFR <60 ml/min) was three times higher in individuals with serum homocysteine in the tertile than in those in the lowest tertile.[44] Plasma homocysteine concentration increases as renal function worsens,[45] typically ranging between 20 and 50 μmol/l in patients who reach ESRD. The increase in plasma concentration associated with moderate renal insufficiency is about 5 μmol/l. Such an increase may be important because in a meta-analysis by Wald *et al.*,[46] a 5 μmol/l higher plasma homocysteine was associated with a 42% higher risk of coronary heart disease death. We reviewed seven prospective observational studies in ESRD, including more than 1000 hemodialysis and 176 continuous ambulatory peritoneal patients. We looked at the relationship between homocysteine and mortality and/or cardiovascular events, and we noted positive and negative associations.[47] Disparate results in these studies contrast with experimental findings indicating that this sulfur amino acid is vasculotoxic. As homocysteine circulates bound to albumin, negative associations, rather than negating its vasculotoxicity, might reflect the deleterious effects of malnutrition. In a study in hemodialysis patients that excluded patients with heart failure at baseline (heart failure is a frequent (30%) cause of severe malnutrition in the dialysis population), homocysteine was unrelated to all-cause mortality but strongly associated with incident atherothrombotic events.[48] The problem is similar to that posed by excessive interdialysis weight gain, which is both an expression of excessive cyclic volume overload (and therefore a strong cardiovascular risk factor) and an indicator of adequate nutrition. In one study, interdialysis weight gain,[49] was inversely rather than directly related to mortality in these patients. Ongoing intervention studies, like the FAVORIT trial (http://www.cscc.unc.edu/favorit/favdescrip.htm), will establish whether homocysteine lowering decreases cardiovascular complications in renal transplant patients and will provide also information useful to the treatment of patients with CKDs.

C-reactive protein and other atherogenic mechanisms triggered by inflammation

The link between inflammation (as measured by C-reactive protein (CRP)) and renal function is established at an early stage in chronic renal disease. This association was well demonstrated in the PREVEND study.[50] In this study, patients were stratified into four quartiles according to serum CRP. When these quartiles were related to creatinine clearance, even though creatinine clearance was on average in the normal range in all quartiles, it was significantly less in patients with high CRP (fourth quartile) than in those with low CRP (first quartile) (Figure 1). Although a recent meta-analysis suggests that the role of serum CRP as a risk factor in the general population might have been overemphasized,[51] considerations in the general populations do not apply to chronic renal insufficiency, a high-risk population where CRP most often signals a severe degree of target organ damage (see below). There is still a lack of intervention studies that lowering CRP may retard renal disease progres-

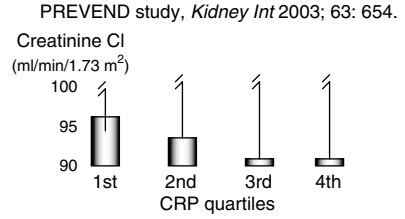

Figure 1 | Relationship between serum CRP and creatinine clearance in the PREVEND study.

sion and reduce cardiovascular complications in patients with CKD. In a secondary analysis of three randomized controlled trials Tonelli found that pravastatin slightly retards (−8%) renal function loss[52] and produces an important decrease in the incidence rate of cardiovascular events (−33%)[53] in patients with or at risk for coronary heart disease. When renal function approaches 0, serum CRP attains very high levels.[54–56] In ESRD, CRP is strongly associated with increased risk of death and cardiovascular events.[57,58] However, atorvastatin failed to reduce cardiovascular events in diabetic uremics on chronic dialysis in the German Diabetes and Dialysis study (4D).[59] Inflammation, a fundamental promoter of atherosclerosis, interacts with many pathophysiologic pathways that lead to vascular damage. *In vitro*, inflammatory cells (monocyte-macrophage) potentiate alkaline phosphatase activity of osteoclast-like cells in the vascular system;[60] this suggests that inflammation favors vascular calcification. In line with this hypothesis, Wang *et al.*[61] showed that cardiac valve calcifications are much more frequent in ESRD patients with high CRP levels than in those with relatively lower levels. Inflammation also interacts with several pro-atherogenic mechanisms. One major inflammatory molecule, interleukin-6, stimulates fibrinogen synthesis via a specific interleukin-6-sensitive sequence in the fibrinogen gene; this pathway leads to thrombosis. Fibrinogen is at center stage in mediating the cardiovascular damage seen in ESRD patients. Of note, recent mechanistic studies by Kaysen and Don[62] suggest that the synthesis rate of this acute-phase reactant is strongly associated with that of albumin, which in turn is linked to plasma volume. In accord with this hypothesis, plasma fibrinogen was directly related to left-atrial volume in an analysis of patients in the Cardiovascular Risk Extended Evaluation (CREED) database.[47] This association cannot be attributed to the confounding effect of diastolic dysfunction on atrial volume because diastolic rate was almost unmodified after statistical adjustment for the *E*/*A* ratio. The association between plasma fibrinogen, concentric LVH[63] and all-cause death and incident cardiovascular events is well established in hemodialysis patients.[64] Thus multiple mechanisms, both inflammation dependent and -independent, cooperate in determining the high atherothrombotic risk of ESRD. The 4D study clearly indicates that intervening with a statin in the terminal, ESRD phase is unlikely to modify the dim cardiovascular prospects of patients with chronic renal diseases.

Sympathetic overactivity

Sympathetic activity measured by direct recording of sympathetic bursts in the peroneal nerve, the most reliable technique for estimating sympathetic nerve activity, is increased and strongly involved in the pathogenesis of hypertension in patients with mild-to-moderate renal insufficiency.[65] While hypertension is seen as an important cause for cardiovascular complications in patients with chronic renal insufficiency, it is not widely realized that increased sympathetic activity per se might be implicated in hypertension and renal disease progression, and an independently trigger cardiovascular events as well. While no evidence yet links sympathetic activity with cardiovascular complications in the pre-dialysis phase, it was shown that plasma norepinephrine is an independent predictor of new cardiovascular events in ESRD patients.[66] The mechanisms responsible for sympathetic overactivity in renal disease are largely unknown. Sleep apnea, a frequent complication of chronic renal insufficiency, is one important mechanism given that sympathetic activity is increased in patients with primary sleep apnea.[67] Thorough elucidation of the relationship between sleep apnea and raised sympathetic activity is important because it was shown that nocturnal hypoxemia triggers cardiovascular events in ESRD.[68] Other mediators of cardiovascular and renal damage induced by sympathetic over-activity remain to be elucidated. I should point out, however, that norepinephrine induces hypertrophy of myocardial cells *in vitro* and this finding is consistent with our clinical observation that the plasma concentration of this catecholamine is strongly and independently associated with concentric LVH in ESRD patients.[69] The adverse effects of high sympathetic activity are intimately associated with altered regulation of the NO system. Reduced NO synthesis might lead to sympathetic overactivity and, in turn, increased sympathetic activity might lead to reduced NO synthesis and endothelial dysfunction.

ENDOTHELIAL DYSFUNCTION AND REDUCED NO SYNTHESIS

The role of endothelium in renal dysfunction in humans is highlighted by our observation that impaired vasodilatory response to acetylcholine (an established hemodynamic marker of endothelial function) is strongly associated with impaired renal function in patients with essential hypertension.[70] Endothelial dysfunction, a pro-atherogenic alteration, is pervasive in chronic renal disease. Among the various factors invoked to explain this alteration, accumulation of the endogenous inhibitor of NO synthase, asymmetric dimethylarginine (ADMA), appears to be of primary importance. This substance accumulates from the very outset of renal disease, when the GFR is normal.[71] ADMA infused intravenously into healthy subjects to bring the plasma concentration of this substance into the pathophysiologic range causes a distinct increase in arterial pressure as well as sodium retention;[72] this finding is consistent with the observation that salt-sensitive individuals exhibit higher plasma ADMA levels than do salt-resistant ones.[73] High ADMA levels can aggravate the inherently limited ability of patients with chronic renal insufficiency to excrete sodium.

An intact NO system is important for preventing renal disease progression in experimental models,[74] and this issue now deserves careful investigation in humans. ADMA accumulation and the ensuing NO inhibition might accelerate renal disease progression. In a recent study, in a cohort of patients with an average age of 71 years ADMA was inversely related to the GFR and predicted progression of

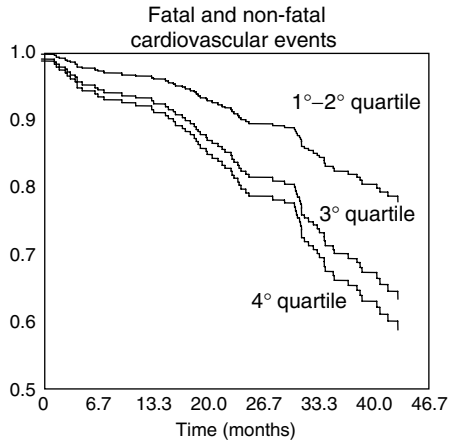

Figure 2 | Relationship between ADMA and cardiovascular events in the CREED study.

renal disease to dialysis.[75] The predictive power of ADMA for renal disease progression is not limited to old patients because almost identical findings have been reported in a middle-aged cohort of CKD patients.[76] In patients with chronic nephropathies ADMA increases linearly with renal function loss[75,76] to reach levels 2–3 times higher than normal in patients with ESRD. Increased ADMA levels are associated with high cardiovascular risk in the general population. In a community level study in Finland, the incidence rate of cardiovascular events in men in the 4th ADMA quartile was 3.9 higher than in those in the other quartiles.[77] The risk associated with high ADMA levels does not flatten out at the pathophysiologic levels. Indeed patients with ESRD, those with the highest ADMA levels, the risk of incident cardiovascular events increased across the whole range of ADMA values[78] (Figure 2).

As I alluded to before, NO influences sympathetic function and vice versa. NO inhibition increases sympathetic activity.[79] In turn, sympathetic activation *in vivo* in humans reduces NO-mediated forearm vasodilation.[80] In ESRD patients these two risk factors may be in the same pathogenic pathway leading to cardiovascular complications. In fact, plasma norepinephrine, a strong and independent predictor of adverse cardiovascular outcomes,[66] loses substantial predictive power in models including plasma ADMA; this suggests that ADMA is a mediator of the atherogenic effects of increased sympathetic activity.[81]

Thus, several novel risk factors other than the traditional Framingham risk factors are present in mild renal insufficiency. Moreover, their adverse impact increases as renal insufficiency worsens.

Preventive strategies

Controlling the epidemic of chronic renal insufficiency should be seen as a part of a large-scale preventive strategy targeting the rising tide of the 'metabolic syndrome' in the general population. Indeed, risk factors for the metabolic syndrome are strongly associated with chronic renal insufficiency at the population level.[82] A healthy lifestyle (in which patients stop smoking; eat foods low in saturated fats, cholesterol, and salt; and participate in regular exercise) might prevent or retard hypertension, hyperlipidemia, and diabetes, thereby preventing or slowing the cardiovascular and renal sequelae of this syndrome. Comprehensive screening programs aimed at detecting individuals at risk for the metabolic syndrome should include GFR and albuminuria measurements to detect disease in the early, asymptomatic phase, and stop it from progressing. In patients with established renal insufficiency, interventions should be taken to prevent further deterioration and to reduce cardiovascular complications.

Hypertension control in patients with renal insufficiency remains unsatisfactory. Indeed, in the Target Blood Pressure Levels in Chronic Kidney Disease survey, as 88% of patients had blood pressure values exceeding target levels recommended by national and international guidelines.[83] In this study, poor compliance with a low-sodium diet and suboptimal prescription of diuretics emerged as major problems in achieving treatment goals. Research aimed at modifying novel risk factors for cardiovascular and renal disease appears of paramount importance in patients with established renal insufficiency. Early treatment of anemia can reduce LVH in patients with progressive renal diseases. The Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study will soon provide an answer to this problem.[84] As discussed, the (4D) suggests that interventions started in ESRD might not be sufficient to prevent cardiovascular events in type 2 diabetics with ESRD. The Study of Heart and Renal Protection (HARP-I)[85] and the Esplanade study will give important information on the role of inflammation in the high rate of cardiovascular events and renal disease progression in patients treated at earlier stages. Likewise, the previously mentioned Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) study assessing the effect of pharmacologic doses of folic acid and vitamins B6 and B12 on cardiovascular risk in transplant patients will provide information that can be extended to patients with CKD.

In addition to research into new and established risk factors, it is important that nephrologists make the best use of knowledge already available to optimize the follow-up of patients with mild renal insufficiency. Guidelines are at central stage in modern medicine. Doctors, patients, health providers, and politicians all perceive the potential impact of clinical practice guidelines implementation on public health. However, implementation and evaluation of guidelines have received only scant attention as compared with development and promulgation. Public health would be much improved if we were able to better apply what we have learned from the blossoming of clinical research studies of the last 30 years or so.[86] We need to identify barriers to the application in everyday clinical practice of coherent, integrated treatments for retarding renal disease progression and for preventing cardiovascular risk. Every effort should be made to streamline

the collaboration between hospital departments and physicians to improve follow-up of high-risk patients, particularly in identifying 'problematic' and/or treatment-resistant patients. New forms of collaboration between clinical and academic centers and physicians ought to be planned and tested, such as, outpatient clinics incorporating cardiorenal clinics for high-risk patients, or well-focused internet services and consultations.

REFERENCES

1. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framinham Study. *Am J Cardiol* 1976; **38**: 46–51.
2. Coresh J, Byrd-Holt D, Astor BC *et al.* Chronic kidney disease awareness, prevalence, and trends among US adults, 1999–2000. *J Am Soc Nephrol* 2005; **16**: 180–188.
3. 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* 2004; **141**: 95–101.
4. Culleton BF, Larson MG, Evans JC *et al.* Prevalence and correlates of elevated serum creatinine levels: the Framingham Heart Study. *Arch Intern Med* 1999; **159**: 1785–1790.
5. Fox CS, Larson MG, Leip EP *et al.* Predictors of new-onset kidney disease in a community based population. *JAMA* 2004; **291**: 844–850.
6. Chadban SJ, Briganti EM, Kerr PG *et al.* Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *J Am Soc Nephrol* 2003; **14**(Suppl 2): S131–8.
7. Pinto-Sietsma SJ, Mulder J, Janssen WM *et al.* Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann Intern Med* 2000; **133**: 585–591.
8. Verhave JC, Gansevoort RT, Hillege HL *et al.* PREVEND Study Group. An elevated urinary albumin excretion predicts de novo development of renal function impairment in the general population. *Kidney Int Suppl* 2004; **92**: S18–S21.
9. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 2005; **16**: 2134–2140.
10. McClellan WM, Ramirez SBP, Jurkovitz C. Screening for chronic kidney disease: unresolved issues. *J Am Soc Nephrol* 2003; **14**(Suppl 2): S81–S87.
11. Perneger TV, Klag MJ, Feldman HI, Whelton PK. Projections of hypertension-related renal disease in middle-aged residents of the United Status. *JAMA* 1993; **269**: 1272–1277.
12. Segura J, Campo C, Gil P *et al.* Development of chronic kidney disease and cardiovascular prognosis in essential hypertensive patients. *J Am Soc Nephrol* 2004; **15**: 1616–1622.
13. McClellan WM, Langston RD, Presley R. Medicare patients with cardiovascular disease have a high prevalence of chronic kidney disease and a high rate of progression to end-stage renal disease. *J Am Soc Nephrol* 2004; **15**: 1912–1919.
14. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; **109**: 1004–1009.
15. Shlipak MG, Smith GL, Rathore SS *et al.* Renal function, digoxin therapy, and heart failure outcomes: evidence from the digoxin intervention group trial. *J Am Soc Nephrol* 2004; **15**: 2195–2203.
16. Culleton BF, Larson MG, Wilson PW *et al.* Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999; **56**: 2214–2219.
17. Manjunath G, Tighiouart H, Ibrahim H *et al.* Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003; **41**: 47–55.
18. Garg AX, Clark WF, Haynes RB, House AA. Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. *Kidney Int* 2002; **61**: 1486–1494.
19. Muntner P, He J, Hamm L *et al.* Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol* 2002; **13**: 745–753.
20. Weiner DE, Tighiouart H, Amin MG *et al.* Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol* 2004; **15**: 1307–1315.
21. Schillaci G, Reboldi G, Verdecchia P. High-normal serum creatinine concentration is a predictor of cardiovascular risk in essential hypertension. *Arch Intern Med* 2001; **161**: 886–891.
22. De Leeuw PW, Thijs L, Birkenhager WH *et al.* Prognostic significance of renal function in elderly patients with isolated systolic hypertension: results from the Syst-Eur trial. *J Am Soc Nephrol* 2002; **13**: 2213–2222.
23. Anavekar NS, McMurray JJ, Velazquez EJ *et al.* Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; **351**: 1285–1295.
24. Go AS, Chertow GM, Fan D *et al.* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **23**: 1296–1305.
25. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol* 1998; **9**: S16–S23.
26. Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the 'only-50%' myth. *Arch Intern Med* 2001; **161**: 2657–2660.
27. Yusuf S, Hawken S, Ounpuu S *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. *Lancet* 2004; **364**: 937–952.
28. Sarnak MJ, Coronado BE, Greene T *et al.* Cardiovascular disease risk factors in chronic renal insufficiency. *Clin Nephrol* 2002; **57**: 327–335.
29. Zoccali C, Mallamaci F, Tripepi G. Traditional and emerging cardiovascular risk factors in end-stage renal disease. *Kidney Int* 2003; **63**(Suppl 85): S105–S110.
30. Locatelli F, Canaud B, Eckardt KU *et al.* Oxidative stress in end-stage renal disease: an emerging threat to patient outcome. *Nephrol Dial Transplant* 2003; **18**: 1272–1280.
31. Zoccali C, Mallamaci F, Tripepi G *et al.* Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. *J Am Soc Nephrol* 2002; **13**: 134–141.
32. Johnson R, Herrera-Acosta J, Schreiner GF, Rodriguez Iturbe B. Mechanisms of disease: subtle acquired renal injury as a mechanism of salt-sensitive hypertension. *N Engl J Med* 2002; **346**: 913–923.
33. Diamond JR. Analogous pathobiologic mechanisms in glomerulosclerosis and atherosclerosis. *Kidney Int* 1991; **31**(Suppl): S29–S34.
34. Brocco E, Fioretto P, Mauer M *et al.* Renal structure and function in non-insulin dependent diabetic patients with microalbuminuria. *Kidney Int* 1997; **63**(Suppl): S40–S44.
35. Levin A, Thompson CR, Ethier J *et al.* Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999; **34**: 125–134.
36. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. *Kidney Int* 2004; **66**: 753–760.
37. Iaina A, Silverberg DS, Wexler D. Therapy insight: congestive heart failure, chronic kidney disease and anemia, the cardio-renal-anemia syndrome. *Nat Clin Pract Cardiovasc Med* 2005; **2**: 95–100.
38. Volkova N, Arab L. Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. *Am J Kidney Dis* 2006; **47**: 24–36.
39. De Boer IH, Gorodetskaya I, Young B *et al.* The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. *J Am Soc Nephrol* 2002; **13**: 2762–2769.
40. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 2002; **62**: 245–252.
41. Cozzolino M, Brancaccio D, Gallieni M, Slatopolsky E. Pathogenesis of vascular calcification in chronic kidney disease. *Kidney Int* 2005; **68**: 429–436.
42. Ritz E. The clinical management of hyperphosphatemia. *J Nephrol* 2005; **218**: 221–228.
43. Hoogeveen EK, Kostense PJ, Jager A *et al.* Serum homocysteine level and protein intake are related to risk of microalbuminuria: the Hoorn Study. *Kidney Int* 1998; **54**: 203–209.
44. Ninomiya T, Kiyohara Y, Kubo M *et al.* Hyperhomocysteinemia and the development of chronic kidney disease in a general population: the Hisayama study. *Am J Kidney Dis* 2004; **44**: 437–445.
45. Chauveau P, Chadefaux B, Coude M *et al.* Hyperhomocysteinemia, a risk factor for atherosclerosis in chronic uremic patients. *Kidney Int* 1997; **41**(Suppl): S72–S77.
46. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 2002; **325**: 1202.
47. Zoccali C, Enia G, Tripepi G *et al.* Clinical epidemiology of non-traditional risk factors in peritoneal dialysis patients. *Peritoneal Dial Int* 2005; **25**(Suppl 3): S84–S87.
48. Mallamaci F, Zoccali C, Tripepi G *et al.* Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. *Kidney Int* 2002; **61**: 609–614.

49. Sezer S, Ozdemir FN, Arat Z *et al.* The association of interdialytic weight gain with nutritional parameters and mortality risk in hemodialysis patients. *Ren Fail* 2002; **24**: 37–48.
50. Stuveling EM, Hillege HL, Bakker SJ *et al.* C-reactive protein is associated with renal function abnormalities in a non-diabetic population. *Kidney Int* 2003; **63**: 654–661.
51. Danesh J, Wheeler JG, Hirschfield GM *et al.* C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004; **350**: 1387–1397.
52. Tonelli M, Isles C, Craven T *et al.* Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. *Circulation* 2005; **112**: 171–178.
53. Tonelli M, Isles C, Curhan GC *et al.* Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* 2005; **110**: 1557–1563.
54. Landray MJ, Wheeler DC, Lip GY *et al.* Inflammation, endothelial dysfunction, and platelet activation in patients with chronic kidney disease: the chronic renal impairment in Birmingham (CRIB) study. *Am J Kidney Dis* 2004; **43**: 244–253.
55. Zimmermann J, Herrlinger S, Pruy A *et al.* Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 1999; **55**: 648–658.
56. Zoccali C, Benedetto FA, Mallamaci F *et al.* Inflammation is associated with carotid atherosclerosis in dialysis patients. Creed investigators. Cardiovascular risk extended evaluation in dialysis patients. *J Hypertens* 2000; **18**: 1207–1213.
57. Stenvinkel P, Wanner C, Metzger T *et al.* Inflammation and outcome in end-stage renal failure: does female gender constitute a survival advantage? *Kidney Int* 2002; **62**: 1791–1798.
58. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2000; **35**: 469–476.
59. Wanner C, Krane V, Marz W *et al.* German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353**: 238–248.
60. Tintut Y, Patel J, Territo M *et al.* Monocyte/macrophage regulation of vascular calcification *in vitro*. *Circulation* 2002; **105**: 650–655.
61. Wang AY, Wang M, Woo J *et al.* Cardiac valve calcification as an important predictor for all-cause mortality and cardiovascular mortality in long-term peritoneal dialysis patients: a prospective study. *J Am Soc Nephrol* 2003; **14**: 159–168.
62. Kaysen GA, Don BR. Factors that affect albumin concentration in dialysis patients and their relationship to vascular disease. *Kidney Int* 2003; **63**(Suppl 84): S94–S97.
63. Zoccali C, Benedetto F, Mallamaci F *et al.* Fibrinogen, inflammation and concentric left ventricular hypertrophy in chronic renal failure. *Eur J Clin Invest* 2003; **33**: 561–566.
64. Zoccali C, Mallamaci F, Tripepi G *et al.* Fibrinogen, mortality and incident cardiovascular complications in end-stage renal failure. *J Intern Med* 2003; **254**: 132–139.
65. Ligtenberg G, Blankestijn PJ, Oey PL *et al.* Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure. *N Engl J Med* 1999; **340**: 1321–1328.
66. Zoccali C, Mallamaci F, Parlongo S *et al.* Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 2002; **105**: 1354–1359.
67. Narkiewicz K, Somers VK. Sympathetic nerve activity in obstructive sleep apnoea. *Acta Physiol Scand* 2003; **177**: 385–390.
68. Zoccali C, Mallamaci F, Tripepi G. Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. *J Am Soc Nephrol* 2002; **13**: 729–733.
69. Zoccali C, Mallamaci F, Tripepi G *et al.* Norepinephrine and concentric hypertrophy in patients with end-stage renal disease. *Hypertension* 2002; **40**: 41–46.
70. Perticone F, Maio R, Tripepi G, Zoccali C. Endothelial dysfunction and mild renal insufficiency in essential hypertension. *Circulation* 2004; **17**: 821–825.
71. Kielstein JT, Boger RH, Bode-Boger SM *et al.* Marked increase of asymmetric dimethylarginine in patients with incipient primary chronic renal disease. *J Am Soc Nephrol* 2002; **13**: 170–176.
72. Kielstein JT, Impraim B, Simmel S *et al.* Cardiovascular effects of systemic nitric oxide synthase inhibition with asymmetrical dimethylarginine in humans. *Circulation* 2004; **109**: 172–177.
73. Fujiwara N, Osanai T, Kamada T *et al.* Study on the relationship between plasma nitrite and nitrate level and salt sensitivity in human hypertension: modulation of nitric oxide synthesis by salt intake. *Circulation* 2000; **101**: 856–861.
74. Klahr S. The role of nitric oxide in hypertension and renal disease progression. *Nephrol Dial Transplant* 2001; **16**(Suppl 1): 60–62.
75. Ravani P, Tripepi G, Malberti F *et al.* Asymmetrical dimethylarginine predicts progression to dialysis and death in patients with chronic kidney disease: a competing risks modeling approach. *J Am Soc Nephrol* 2005; **16**: 2449–2455.
76. Fliser D, Kronenberg F, Kielstein JT *et al.* Asymmetric dimethylarginine and progression of chronic kidney disease: the mild to moderate kidney disease study. *J Am Soc Nephrol* 2005; **16**: 2456–2461.
77. Valkonen VP, Paiva H, Salonen JT *et al.* Risk of acute coronary events and serum concentration of asymmetrical dimethylarginine. *Lancet* 2001; **358**: 2127–2128.
78. Zoccali C, Bode-Boger S, Mallamaci F *et al.* Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study. *Lancet* 2001; **358**: 2113–2117.
79. Travagli RA, Gillis RA. Nitric oxide-mediated excitatory effect on neurons of dorsal motor nucleus of vagus. *Am J Physiol* 1994; **266**: G154–G160.
80. Hijmering ML, Stroes ES, Olijhoek J *et al.* Sympathetic activation markedly reduces endothelium-dependent, flow-mediated vasodilation. *J Am Coll Cardiol* 2002; **39**: 683–688.
81. Mallamaci F, Tripepi G, Maas R *et al.* Analysis of the relationship between norepinephrine and asymmetric dimethyl arginine levels among patients with end-stage renal disease. *J Am Soc Nephrol* 2004; **15**: 435–441.
82. Chen J, Muntner P, Hamm LL *et al.* The metabolic syndrome and chronic kidney disease in US adults. *Ann Intern Med* 2004; **140**: 167–174.
83. De Nicola N, Minutolo R, Chiodini P *et al.* Global approach to cardiovascular risk in chronic kidney disease. *Kidney Int* 2006; **69**: 538–545.
84. Eckardt KU. Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) Trial. The CREATE trial – building the evidence. *Nephrol Dial Transplant* 2001; **16**(Suppl 2): 16–18.
85. Baigent C, Landray M, Leaper C. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *Am J Kidney Dis* 2005; **45**: 473–484.
86. Lenfant C. Shattuck lecture. Clinical research to clinical practice: lost in translation? *N Engl J Med* 2003; **49**: 868–874.