

Chronic kidney disease and cardiovascular disease

Coronary vascular disease is the leading cause of death in patients with end-stage renal disease.

SUMAN MAHARAJ, MB ChB, FCP (SA)

Fellow in Nephrology, Inkosi Albert Luthuli Central Hospital

Consultant in Internal Medicine: Nelson R Mandela School of Medicine, Durban

Suman Maharaj is a senior registrar in the Department of Nephrology at Inkosi Albert Luthuli Central Hospital in Durban. He completed his undergraduate studies in 1999 at the University of Natal and his Fellowship examination in 2005. His fields of interest include cardiac disease in the chronic kidney patient, immunologically mediated kidney diseases and transplant medicine.

D P NAIDOO, MB ChB, FRCP

Head and Professor of Cardiology, Inkosi Albert Luthuli Central Hospital, Durban

Professor Naidoo is Head of the Department of Cardiology, Inkosi Albert Luthuli Central Hospital and Nelson R Mandela School of Medicine, Durban. His fields of interest include hypertension, echocardiography, teaching and research.

Cardiovascular disease (CVD) is the leading cause of death in patients with end-stage renal disease (ESRD) worldwide and accounts for approximately 30 - 50% of all deaths. It is a sobering fact that the risk for premature CVD in a 30-year-old patient with ESRD is similar to that of a 70 - 80-year-old without chronic kidney disease (CKD).

It is unclear how much of the association between kidney and vascular disease results from

- vascular disease causing kidney failure
- kidney failure causing vascular disease or
- the common underlying factors that promote the progression of CKD and CVD.

The prevalence of CVD is increased among patients in all stages of CKD (Table I) and early CKD is a well-established independent risk factor for an adverse cardiovascular outcome (Fig. 1). This relationship becomes exponential as glomerular filtration rate (GFR) declines below 45 ml/min. Consequently, patients with reduced renal function are more likely to die from CVD than they are likely to develop ESRD.

The outlook among the ESRD population is much worse. Only 16% of new dialysis patients have normal hearts. On starting dialysis therapy, the prevalence of cardiomyopathy is high, as is the presence of ischaemic heart disease, left ventricular hypertrophy (LVH) and heart failure. This high prevalence of CVD on starting dialysis suggests that the predialysis phase of CKD is a state of high cardiac risk.

Spectrum of CVD in patients with CKD

The spectrum of cardiac involvement in CKD involves 3 main pathological forms:

- altered cardiac geometry and mechanics
- atherosclerosis
- arteriosclerosis.

Left ventricular (LV) remodelling is pervasive in CKD and is due to various genetic, mechanical and neurohormonal factors, which alter LV size, shape and function and result in LVH with its associated cardiovascular sequelae. As GFR declines the prevalence

Table I. Stages of chronic kidney disease

Stage 1: Kidney damage (pathological abnormalities or markers of damage including abnormalities in blood or urine tests or in imaging studies) with normal or raised glomerular filtration rate (≥ 90 ml/min/1.73 m ²)
Stage 2: Glomerular filtration rate 60 – 89 ml/min/1.73 m ² with evidence of kidney damage
Stage 3: Glomerular filtration rate 30 – 59 ml/min/1.73 m ²
Stage 4: Glomerular filtration rate 15 – 29 ml/min/1.73 m ²
Stage 5: End-stage renal failure, glomerular filtration rate < 15 ml/min/1.73m ²

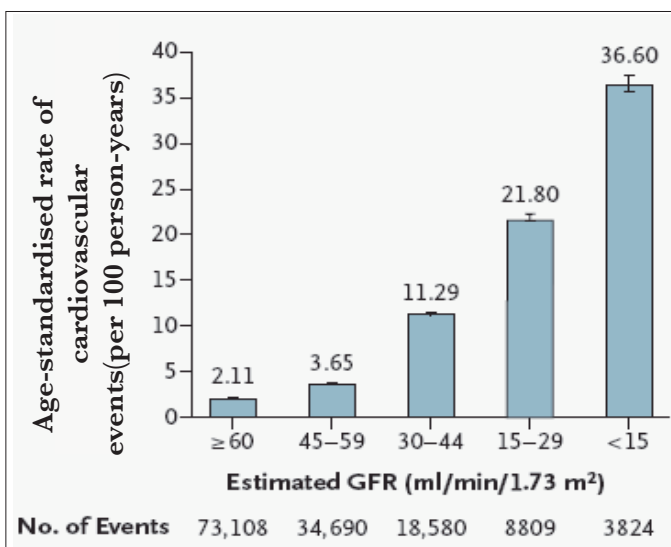


Fig. 1. Rate of CVD events as a function of GFR.¹

Vascular remodelling is a pathological hallmark of CKD, affecting the large arteries as well as the coronary vessels.

of LVH increases and is associated with a rise in cardiovascular mortality.

Atherosclerosis of coronary arteries is the primary cause of ischaemic heart disease in patients with CKD, with acute myocardial infarction accounting for 20% of all cardiac deaths. The coronary plaque in dialysis patients is a more advanced and complex lesion, characterised by greater degrees of medial thickening and calcification. However, a significant number (27 - 50%) of patients with ESRD who experience angina do not have large-vessel disease. Here, microvascular atherosclerosis, severe LVH and anaemia are thought to be the causative factors.

Vascular remodelling is a pathological hallmark of CKD, affecting the large arteries as well as the coronary vessels. In part, this is due to medial calcification, which reduces compliance and manifests as an increase in pulse pressure with systolic hypertension. This process contributes to aortic stiffness, LVH and myocardial infarction, and parallels the increase in cardiovascular morbidity and mortality in the CKD patient.

Cardiovascular risk factors in the CKD population (Table II)

Although the association between CKD and cardiovascular risk was first shown in patients with ESRD, it is now well established that overt proteinuria (urine protein > 300 mg/day), with preserved renal function, is an established risk factor for atherosclerotic CVD (Fig. 2). Even microalbuminuria (urine albumin excretion: 30 - 299 mg/day) has been recognised as a simple marker of atherosclerosis, and is independently predictive of cardiovascular morbidity and mortality. Microalbuminuria probably reflects subclinical vascular damage in the kidneys and other vascular beds, and may also signify systemic endothelial dysfunction that predisposes to future cardiovascular events.

Furthermore, diabetic patients with ESRD have a higher cardiovascular mortality than non-diabetic ESRD patients. In fact, up to 50% of diabetics undergoing pre-transplant evaluation will have significant coronary artery disease (CAD) (i.e. > 50% stenosis in one or more vessels). Diabetes itself and non-diabetic CKD share many of the pathogenic risk factors that account for this

excess mortality. These include proteinuria, endothelial dysfunction, increased oxidant stress and dyslipidaemia (see below). Both diabetes and CKD are associated with medial calcification, LVH and accelerated atherosclerosis. Hence, the combination of both diabetes and CKD portends an additive poor cardiac risk. This is exemplified by studies which have shown that both increased carotid intima-media thickness and increased aortic stiffness (both of which independently predict cardiovascular mortality) are more prevalent in diabetic CKD than either diabetes or non-diabetic CKD alone.

Certain uraemia-related risk factors, such as anaemia, altered calcium/phosphate homeostasis, vascular inflammation and oxidant stress, also contribute to the accelerated atherosclerosis and maladaptive vascular remodelling among the CKD population.

Anaemia in the presence of less severe renal dysfunction (creatinine clearance: 25 - 75 ml/min) is associated with LVH, and more severe anaemia in the ESRD patient is associated with LV dilation, cardiac failure and death.

The prevalence and severity of cardiovascular calcification (CVC) is increased in patients with ESRD. The exact mechanism is unknown, but an imbalance between promoters and inhibitors of calcification is postulated (Table III). Aside from traditional Framingham risk factors, a high Ca/PO₄ product is a potent promoter of CVC. Calcification involves the large arteries, coronary vessels and cardiac valves. Medial calcification leads to increased pulse pressure, increased afterload, reduced coronary perfusion, myocardial infarction, cardiac failure and death. Valvular calcification may lead to stenosis, arrhythmias, heart failure, and infective endocarditis.

Attempts to reverse this calcification process (with the use of novel phosphate binders and calcimimetics) are still in the experimental phases of study.

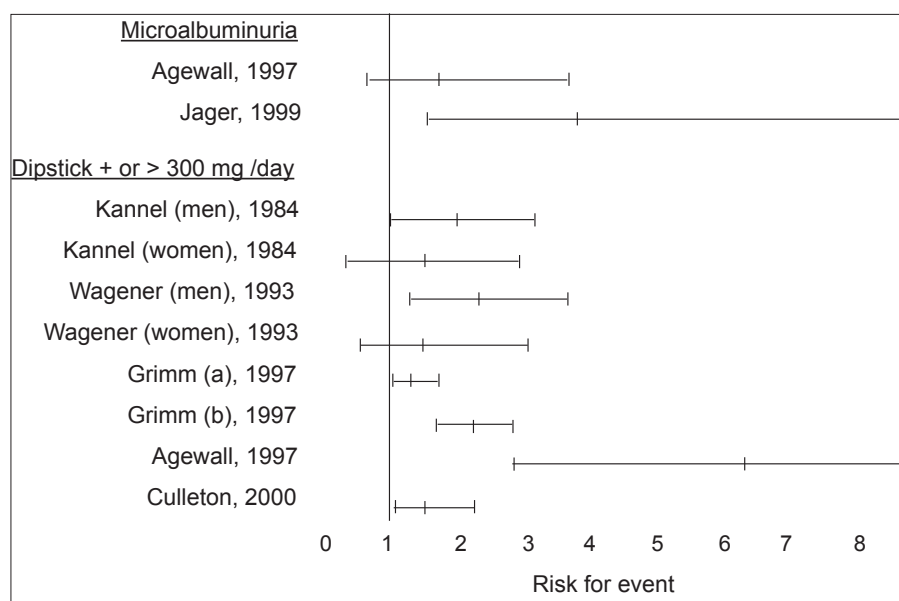


Fig. 2. Proteinuria and relative risk for cardiovascular death.²

Table II. Cardiovascular risk factors in chronic kidney disease

Traditional major risk factors	Factors unique to CKD
Diabetes	Microalbuminuria/proteinuria
Hypertension	Anaemia
Raised LDL-C	Altered calcium/phosphate homeostasis
Cigarette smoking	Volume overload
Left ventricular hypertrophy	Sympathetic overactivity
	Increased oxidant stress
	Increased vascular inflammation
	Lp(a)

Table III. Novel factors involved in vascular calcification in the CKD patient

Promoters	Inhibitors
High Ca/PO ₄ product	Fetuin A
Uraemic serum	BMP-7
Vitamin D therapy	Matrix gla protein
Hyperparathyroidism	Osteopontin
Chronic inflammation	Osteoprotegerin
LDL-C	HDL

Pathogenesis of vascular injury in CKD

In addition to the traditional risk factors, accelerated atherosclerosis peculiar to CKD involves the three related processes of vascular inflammation, oxidative stress and vascular calcification, all of which result in vascular remodelling. Oxidative stress has a central role in the pathogenesis of atherosclerosis and CKD is associated with an imbalance favouring pro-oxidant over antioxidant systems, contributing to the increased atherosclerotic burden. Serum C-reactive protein (CRP) is a reliable marker of atherosclerotic complications. Both CRP and thrombogenic factors, such as fibrinogen, are also elevated in patients with ESRD, and are strong predictors of death and adverse cardiovascular events.

Declining renal function itself is also associated with an inflammatory response, manifested by an increase in pro-inflammatory cytokines in both early and advanced CKD. Increased levels of the pro-atherogenic cytokine, IL-6, are independently associated with carotid atherosclerosis and predict mortality in dialysis patients.

Diagnosis of CVD in the CKD patient

Diagnosis is difficult as a significant number of patients (up to 50%) are asymptomatic, suffering silent ischaemia. This is seen particularly in diabetics and the elderly. Uraemia itself is known to alter sympathetic responses and contributes to the silent ischaemia that is often observed in younger ESRD patients without diabetes.

Diagnosis is compounded by the fact that exercise electrocardiography is neither sensitive nor specific – interpretation is hampered by electrolyte abnormalities, conduction defects, uraemic pericarditis and LVH, all of which distort the baseline electrocardiogram. Furthermore, patients are often unable to exercise maximally,

due to peripheral neuropathy, peripheral vascular disease and poor effort tolerance.

Therefore, coronary angiography remains the gold standard for the detection of epicardial CAD, but complication rates tend to be higher among the CKD population. These include con-trast nephropathy, athero-embolism, bleed-ing complications and contrast-induced pulmonary oedema. In the predialysis patient undergoing coronary angiography, the risk may be enough to precipitate ESRD as a result of the procedure itself.

There are also limitations to angiography. It is of little value in diagnosing microvascular CAD. Secondly, more than a quarter of ESRD patients with typical angina who undergo angiography have normal or minimal CAD. Consequently, there is still a need for a safe, non-invasive, diagnostic modality that will allow stratification of cardiovascular risk among the CKD population. Here, myocardial perfusion studies and dobutamine stress echocardiography have undergone extensive evaluation among the ESRD population. In a recent meta-analysis the sensitivity and specificity for both these tests in predicting coronary stenoses was

only about 60%. Therefore a negative study should be interpreted with caution in the high-risk patient.

Coronary angiography might be the gold standard for the diagnosis of epicardial CAD. However, in a resource-limited country like South Africa, it may not be feasible to subject all medium- and high-risk patients to angiography. Furthermore, whether a long history of diabetes constitutes high risk or not, is debatable, and the decision to proceed to angiography may best be individualised. Recognising all these limitations, our current recommendations for the diagnostic evaluation of ischaemia in the CKD and ESRD patient employ a risk stratification approach (Fig. 3).

In a resource-poor setting like the South African state sector, patients with CAD are not offered renal replacement therapy (RRT), including dialysis or transplantation. However, in the authors' opinion, those patients with mild disease (single vessel) should be offered a revascularisation procedure first, and should then be reassessed for transplant suitability. Patients with advanced disease (double/triple vessel) have significant vascular involvement and multisystem disease. As the commonest cause of graft loss in these circumstances is cardiovascular death, transplantation would lead to allograft wastage, and therefore cannot be recommended. Palliative dialysis then becomes the therapy of choice.

Elderly patients (> 60 years) with ESRD have a higher incidence of CVD, and RRT is currently an exclusion criterion in the South African state sector. Notwithstanding the ethical considerations surrounding this issue, there are sufficient data available to demonstrate that these patients do

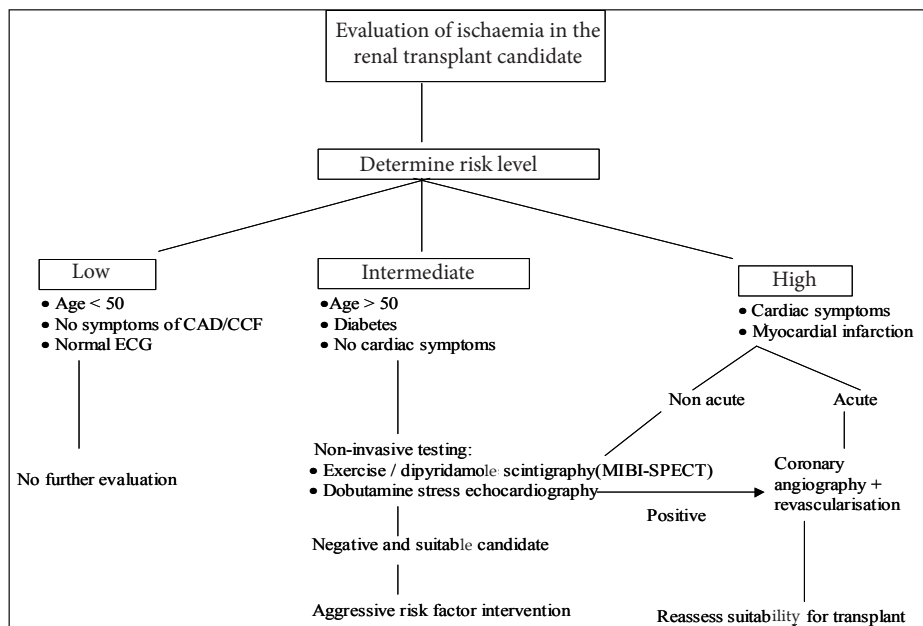


Fig. 3. Risk stratification approach to the diagnostic evaluation of ischaemia in the CKD and ESRD patient.

Correction of anaemia is associated with regression of LVH, resolution of angina and a reduction in cardiovascular mortality.

benefit from renal transplantation. In these circumstances the use of marginal kidneys may be more appropriate and therefore our selection criteria should be expanded to accept the so-called elderly onto RRT programmes in South Africa.

Newer modalities

Over the last decade, cardiac CT has been studied as an alternative to invasive coronary angiography in the diagnosis of CAD. Although electron beam computed tomography (EBCT) cannot detect individual obstructive lesions, it has a high sensitivity for the detection of coronary artery calcification (CAC). Among the general population, CAC scores correlate with plaque burden and vessel stenosis, and high scores are predictive of future cardiac events. This correlation among the ESRD population is less well established. Higher CAC scores have been found to be more prevalent among patients with stage 3 - 5 CKD, and rapidly progressive CAC scores in the dialysis population is a well-described phenomenon. It is not clearly established whether a high CAC score represents medial vascular calcification associated with arteriosclerosis (a feature of CKD) or intimal calcification (a feature of atherosclerosis) or both. Although total CAC scores do correlate with the number and severity of

angiographically proven diseased vessels, there are no long-term follow-up data available to determine if increased scores correlate with an adverse cardiac outcome.

A more suitable imaging modality may be modern-day 64-slice coronary CT scanning. Several recent studies among the general population have shown it to have an excellent diagnostic accuracy for the detection of significant stenosis in even the smaller coronary arteries as well as side branches, with sensitivities and specificities ranging from 86% to 95% and 93% to 97% respectively. With a high negative predictive value of 95 - 97%, multidetector CT can reliably exclude a haemodynamically significant stenosis as well.

There have been no published data regarding the clinical utility of coronary CT angiography in the diagnostic evaluation of the patient with CKD. The procedure is also not without risk, since it involves the injection of contrast. However, in the patient on maintenance dialysis, this risk would be of little significance.

Since invasive coronary angiography may not be accompanied by any percutaneous intervention the procedure places patients at an unnecessary risk for complications such as bleeding, perforation and athero-embolism.

Coronary CT angiography is not associated with these complications, and the promising results in the non-ESRD population make it an attractive area for future study.

Management of cardiovascular risk in the CKD/ESRD patient (Table IV)

Approximately 75% of patients with CKD have hypertension, the prevalence of which increases as GFR declines. Since lowering blood pressure decreases cardiovascular morbidity and mortality and slows CKD progression, control of blood pressure to target levels is of paramount importance. Lower target levels are recommended (< 130/80 mmHg) in CKD and even lower levels (< 125/75 mmHg) should be attained in patients with significant proteinuria. To achieve these targets, at least 3 - 4 medications are often required.

Control of proteinuria and the inhibition of the renin-angiotensin system are important in slowing the progression of diabetic and non-diabetic CKD. Whether the renoprotection offered by the use of ACE inhibitors and angiotensin receptor blockers is due to their antihypertensive or antiproteinuric effects, or both, is still controversial. However, their use is associated with regression of LVH, reduction in cardiovascular morbidity and mortality, reduction in proteinuria and a slower progression to ESRD in diabetic and non-diabetic CKD.

Table IV. Targets for risk factor reduction in CKD³

Factor	Target	Recommended therapy
Hypertension	Proteinuria < 1 g/d; BP < 130/80 mmHg Proteinuria > 1 g/d; BP < 125/75 mmHg	Initially: ACE inhibitor plus salt restriction + diuretic. Add angiotensin II receptor blocker or non-dihydropyridine calcium channel blocker. Refer if BP still not controlled
Proteinuria	< 1 g/d	Use an ACE inhibitor or angiotensin II receptor blocker alone or in combination; titrate to control proteinuria even if blood pressure target is achieved
Blood glucose (in DM)	Haemoglobin A _{1c} : 7 - 8%	Type 1 DM: insulin Type 2 DM: sulphonylureas (GFR > 60 ml/min); biguanides (GFR > 30 ml/min); insulin (GFR < 30 ml/min)
Dyslipidaemia	Total cholesterol < 5.17 mmol/l LDL cholesterol < 3.10 mmol/l	Statin
Anaemia	Maintain haemoglobin above 11 g/dl Avoid fall below 10 g/dl	Correct haematinic deficiencies Parenteral iron in CKD stage 4 - 5 Erythropoietin in CKD stage 4 - 5
Hyperparathyroidism/renal osteodystrophy	Serum calcium > 2.2 mmol/l Serum phosphate < 1.8 mmol/l Serum PTH between 1 and 2 × normal	Calcium and vitamin D supplementation Reduce phosphate intake to ≈ 800 mg/d

Cardiovascular disease

Tight diabetic control not only slows progression of diabetic nephropathy, but is also associated with a lower risk of macrovascular disease, including ischaemic heart disease (IHD) and peripheral vascular disease. Metformin is of benefit for macrovascular disease in obese type 2 diabetics, but is contraindicated in the later stages of CKD (GFR < 30 ml/min).

The direct lipid-lowering effects of statins are known to reduce cardiovascular risk. However, their pleiotropic effects, independent of lipid lowering, are postulated to have beneficial cardiovascular effects as well. These include stabilisation of endothelial function and anti-thrombogenic and anti-inflammatory properties, thus targeting the key factors involved in the

pathogenesis of atherosclerosis. These effects justify their use in CKD patients with high cardiovascular risk.

Correction of anaemia is associated with regression of LVH, resolution of angina and a reduction in cardiovascular mortality. Attention should also focus on controlling hyperparathyroidism, which reduces the risk of cardiovascular calcification and prevents bone marrow fibrosis, which is associated with erythropoietin-resistant anaemia.

Summary

The aim of this article is to reinforce the importance of early detection of CKD, not only to slow the progression to ESRD, but also to identify cardiovascular disease,

the major determinant of mortality among the CKD population. Currently the management of CKD in South Africa is suboptimal – it is hoped that with an aggressive multifactorial risk factor modification programme coupled with a rational pharmacological approach, we may halt the devastating course of CKD.

References

1. Alan, *et al.* Rate of cardiovascular events as a function of glomerular filtration rate. *NEJM* 2004; 351: 296-305.
2. Proteinuria and relative risk for cardiovascular death. KDOQI Clinical Practice Guidelines: NKF, 2002.
3. Targets for risk factor reduction in chronic kidney disease. KDOQI Clinical Practice Guidelines: NKF, 2002.

In a nutshell

- CVD is the leading cause of death in patients with CKD.
- The risk of CVD increases as CKD progresses to ESRD.
- Clinicopathological manifestations of CVD in CKD are:
 - accelerated atherosclerosis
 - left ventricular hypertrophy
 - systolic hypertension.
- 'Uraemia-related' risk factors add to the increased CVD risk.
- Exercise electrocardiography is a suboptimal test for the diagnosis of CVD.
- Coronary angiography is still the gold standard for diagnosis of CAD.
- Achieving targets for risk factors in CKD slows progression of CKD and lowers CVD risk.

single suture

A glass a day

An Italian study of elderly people suggests that those with mild cognitive impairment should drink a glass of wine a day. The study, a longitudinal study of 1 445 ageing Italians who did not have cognitive impairment and 121 with mild cognitive impairment, showed that, compared with total abstinence, those who drank a glass of wine a day may reduce their progression to full-blown dementia. Moderate drinking, defined as less than one glass a day, was also associated with decreased progression to dementia compared with total abstinence. The study does not say whether red or white wine is preferred.

Solfizzi V, *et al.* *Neurology* 2007; 68: 1790-1799.