# Renal dysfunction: a novel indicator and potential promoter of cardiovascular risk

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**ABSTRACT – Epidemiological studies have defined a number of risk factors predicting cardiovascular events, including hypertension, dyslipidaemia, diabetes mellitus and smoking. Renal dysfunction, however, has only recently been included among the strongest predictors of cardiovascular risk.[1] The increment in risk is already apparent in the early stages of borderline renal dysfunction, for example low rates of albumin excretion (microalbuminuria) and minor decrease of creatinine clearance. The information is incomplete, but a number of potential mechanisms have been identified through which renal dysfunction may increase the cardiovascular risk.[2,3] Great progress has been made in providing algorithms to detect patients at risk and to identify interventions to reduce the risk.**

**KEY WORDS: atherosclerosis, blood pressure, cardiovascular risk, microalbuminuria, renal failure**

The Framingham study and many subsequent studies identified a number of classical cardiovascular risk factors such as hypertension, dyslipidaemia, diabetes mellitus and smoking. Renal dysfunction was not included in any of these early studies. The mortality of patients on renal replacement therapy, particularly haemodialysis, was higher by a factor of 10–100 than that of a matched background population.[1] It had not been appreciated that the increase in cardiovascular risk starts early in the evolution of renal disease at levels of serum creatinine (or endogenous creatinine clearance) and albumin excretion rates (microalbuminuria) not previously thought to be associated with increased cardiovascular risk. In recent years, a large body of evidence has been accumulated establishing beyond reasonable doubt that the onset of cardiac disease and the lethality of acute myocardial infarction (AMI) are strikingly increased at even minor degrees of renal dysfunction. Loss of renal function causes hyperfiltration in residual nephrons, so such minor increases in serum creatinine (eg 1.3–1.5 mg/dl) indicate substantial loss of nephrons. Many abnormalities occur at this early stage of renal dysfunction that are potentially relevant for the higher cardiovascular risk such as a rise of blood pressure within the range of normotension,[4] increased lipoprotein (a)[5] or higher concentrations of asymmetric diethyl-L-arginine, an inhibitor of nitric oxide synthase.[6]

## Minor renal dysfunction predicts a high cardiovascular risk in the general population

The Framingham study was the first longitudinal study to identify minor renal dysfunction as a predictor of cardiovascular risk.[7] Mortality rates in men with serum creatinine 1.4–3.0 mg/dl were significantly higher than in controls, but there was no significant difference in women.

These early observations have recently been confirmed in NHANES II (see end of text for explanation of studies).[8] After multivariate analysis, renal insufficiency emerged as a significant predictor of subsequent deaths resulting from cardiovascular disease. In the HOORN study[9] the association of mild renal failure and cardiovascular risk persisted even when corrected for established risk factors such as homocystine, urinary albumin excretion, von Willebrand factor, C-reactive protein and soluble vascular cell adhesion molecule-1 (sVCAM-1). For each 5 ml/min decrease in glomerular filtration rate (GFR) the cardiovascular risk was increased by 26%.

Some information is available from the UK.[10] In a retrospective analysis of 7,690 men followed for an average of 15 years those with a serum creatinine concentration above 1.3 mg/dl (n = 343) had a 60% higher risk of stroke; this persisted after correction for other cardiovascular risk factors. The risk of total mortality, cardiovascular mortality and ischaemic cardiac events was 20% higher in patients with baseline serum creatinine above 1.6 mg/dl than in individuals with lower serum creatinine levels.

In summary, a minor elevation of serum creatinine is associated with an increased cardiovascular risk.

## Does minor renal insufficiency predict the cardiovascular risk in patients at high risk of atherosclerosis?

The earlier studies chose randomly selected individuals from the general population, but information

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has recently become available in populations at high cardiovascular risk, for example from the HOPE study[11] in which ramipril was compared with placebo in patients at high risk of cardiovascular events. Patients with serum creatinine of 1.4–2.3 mg/dl (n = 980) and below 1.4 mg/dl (n = 8,307) were compared. Patients with calculated creatinine clearances below and above 65 ml/min were also compared (for algorithm, see below[12]).

The cumulative prevalence of cardiovascular death, AMI and stroke was higher in individuals with serum creatinine above 1.4 mg/dl than in those with lower values (22.2% vs 15.1% or 55 events vs 36 events per 1,000 patient years). There was a linear increase of risk with serum creatinine values: for increasing quartiles of serum creatinine, the cardiovascular events per 1,000 patient years increased from 33 to 39, 38 and 55. Both cardiovascular mortality (11.4% vs 6.6% or 28 events vs 16 events per 1,000 patient years) and total mortality (17.8% vs 10.6% or 43 events vs 25 events per 1,000 patient years) were higher in patients with early renal failure. The adjusted hazard ratio for patients with creatinine clearance below 6 ml/min was 1.4 (95% confidence interval 1.16–1.69), independent of known cardiovascular risk factors.

Diabetes mellitus is well known to confer a high cardiovascular risk.[13] It is less widely appreciated that the hazard ratio for minor renal dysfunction is as high as that conferred by diabetes. At least in patients at high cardiovascular risk as in the HOPE study,[11] it follows that minor renal dysfunction is a powerful cardiovascular risk predictor. This finding is of particular relevance since one-third of populations at high cardiovascular risk have diminished renal function.

## The impact of mild renal dysfunction in patients with heart failure and acute coronary syndrome

Hillege *et al*[14] measured haemodynamic and serological risk factors in stable patients with advanced heart failure (New York Heart Association III and IV). Possibly to the surprise of the authors, a follow-up showed that reduced renal function was the best predictor of overall mortality: the lower the GFR at the start of the study, the lower the patient survival. It was also noted that a low GFR following an AMI predicted the development of heart failure.15 Meta-analysis must be taken with a grain of salt, but these data are supported by a meta-analysis by Al Suwaidi of the data of all patients with acute coronary syndrome in recent intervention trials.[16]

A reduced GFR is also a substantial risk factor for poor survival in patients on cardiological intensive care units.[17] In other studies,[18,19] in-hospital mortality after AMI was 2% in patients with normal GFR, and 6%, 14% and 21% in patients with mild, moderate and advanced renal failure, respectively. One-year mortality was 24% in patients with normal renal function and 66% in patients with advanced renal failure. It is true that patients with renal failure received less intervention than is standard practice with thrombolysis, angioplasty or bypass surgery, but this alone is insufficient to account for the dramatic excess mortality. More rigorous implementation of state-of-the-art therapy and greater awareness of the importance of impaired renal function could make a dramatic impact on the prevalence of heart failure and acute coronary syndromes.

## Does mild renal dysfunction increase the cardiovascular risk in patients with arterial hypertension?

Mild renal dysfunction increases the cardiovascular risk of patients with hypertension.[20–23] The HDFP,[20] an interventional trial, followed 10,940 patients with known renal disease and serum creatinine above 1.5 mg% (5.8% of the cohort) and heavy (++) proteinuria (3.1%). During a five-year follow-up there was a linear correlation between serum creatinine and cardiovascular mortality, with a fivefold difference between the subjects with the lowest and highest serum creatinine values. The increase in risk was independent of other risk factors.

The HOT study[21] followed 18,790 patients with arterial hypertension, only a minority of whom (ca 10%) had clinical evidence of atherosclerosis. When baseline serum creatinine concentration was above 1.5 mg/dl, the risk of major cardiovascular events was increased by a factor of 2, and the same was true for total mortality.

## Calculating glomerular filtration rate from the serum creatinine concentration at the bedside

It is increasingly recognised that the serum creatinine concentration is an unreliable index of GFR when the former is markedly increased (eg >1.5 mg/dl). Serum creatinine concentration depends on muscle mass and is greatly influenced by age, gender and catabolism. To circumvent these difficulties, several algorithms have been proposed to calculate an estimated endogenous creatinine clearance, the most popular of which is that of Cockroft and Gault.[12]

$$\frac{(140 - \text{age}) \times \text{body weight (kg)}}{72 \times \text{serum creatinine (mg/100 ml)}} = \text{creatinine clearance (ml/min)}$$

*or*

$$\frac{(140 - \text{age}) \times \text{body weight (kg)}}{0.82 \times \text{serum creatinine (μmol)}} = \text{creatinine clearance (ml/min)}$$

## Conclusion

Whatever the aetiology of the underlying renal disease, even a minor decrease in renal function (in GFR), is a powerful predictor of cardiovascular events.[24] This is of particular importance because mild renal failure is noted in up to 10% and 30% of patients at low[7] and high[11] cardiovascular risk, respectively. Minor renal dysfunction is an excellent clinical indicator of high cardiovascular risk, particularly in the patient without traditional cardiovascular risk factors.

Is this increase of renal function-dependent risk susceptible to therapeutic intervention? There is a note of hope because pharmacological blockade of the renin angiotensin system with ramipril[24] reduced cardiovascular end-points in patients with serum creatinine above 1.4 mg/dl. In this high risk group, the

## Key Points

**Minor renal dysfunction, defined as excretion of albumin in the urine below the conventional detection threshold (microalbuminuria), as well as reduced glomerular filtration rate, recognised from increased serum creatinine concentration or decreased estimated creatinine clearance, cause a dramatic increase in cardiovascular risk**

**The risk is demonstrable in the general population, but is progressively higher in individuals with increasingly elevated cardiovascular risk and particularly in individuals with symptomatic coronary heart disease**

**The outcome of MI (myocardial infarction) or PTCA (percutaneous transluminal angioplasty) is strongly dependent on renal function. This is true even for serum creatinine concentrations as low as 1.4 mg/dl or less**

**The underlying pathomechanisms have not been completely identified, but even interventions of proven benefit are insufficiently provided to individuals with such minor renal dysfunction**

proportional risk reduction was even greater. Similar observations were reported by Hillege *et al.*[14,15] Unfortunately, because angiotensin-converting enzyme (ACE) inhibition may further increase serum creatinine concentrations, many physicians hesitate to use ACE inhibition or angiotensin receptor blockers in patients with mild renal dysfunction. However, the results of several studies[14,15,24] indicate that this fear is unjustified because these patients derive particular cardiovascular benefit from this intervention. Moreover, ACE inhibition prevents further loss of renal function.[25–28] It is true that no results are available of a prospective intervention study which specifically addresses reduction of the cardiovascular risk in patients with mild renal dysfunction. Nevertheless, the data of the post hoc analyses are sufficiently impressive[29] to justify the postulate that, as in patients with diabetes mellitus,[13] patients with mild renal dysfunction deserve intensive cardiovascular risk factor intervention:

- lowering blood pressure to less than 130/80 mmHg
- reducing low-density lipoprotein cholesterol to below 105 mg/dl
- prescribing low-dose acetylsalicylic acid and high-dose ACE inhibitors, and
- advising cessation of smoking and regular physical exercise.[29]

### Trial acronyms

| | |
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| HDFP | Hypertension Detection and Follow-Up Program |
| HOPE | Hope Outcomes Prevention Evaluation |
| HOT | Hypertension Optimal Treatment |
| NHANES II | National Health And Nutrition Examination Survey |

### References


1 Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol* 1999;**10**:1606–15.

2 Diercks GF, van Boven AJ, Hillege JL, de Jong PE *et al.* The importance of microalbuminuria as a cardiovascular risk indicator. A review. *Can J Cardiol* 2002;**18**:525–35.

3 Bakris GL. Microalbuminuria: what is it? Why is it important? What should be done about it? Review. *J Clin Hypertens (Greenwich)* 2001; **3**:99–102.

4 Stefanski M, Schmidt KG, Waldherr R, Ritz E. Early increase in blood pressure and diastolic left ventricular malfunction in patients with glomerulonephritis. *Kidney Int* 1996;**50**:1321–6.

5 Kronenberg F, Kuen E, Ritz E, Junker R *et al.* Lipoprotein (a) serum concentrations and apolipoprotein (a) phenotypes in mild and moderate renal failure. *J Am Soc Nephrol* 2000;**11**:105–15.

6 Kielstein JT, Boger RH, Bode-Boger SM, Frolich JC *et al.* Marked increase of asymmetric dimethylarginine in patients with incipient primary chronic renal disease. *J Am Soc Nephrol* 2002;**13**:170–6.

7 Culleton BF, Larson MG, Wilson PW, Evans JC *et al.* Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999;**56**:2214–9.

8 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**:1486–94.

9 Henry DMA, Kostense PJ, Bos G, Stehouwer CDA. Mild renal insufficiency is associated with increased cardiovascular mortality: the Hoorn Study. *Kidney Int* 2002;**62**:1402–07.

10 Wannamethee SG, Shaper AG, Perry IJ. Serum creatinine concentration and risk of cardiovascular disease: a possible marker of increased risk of stroke. *Stroke* 1997;**28**:557–63.

11 Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 2001;**134**:629–36.

12 Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.

13 Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;**339**:229–34.

14 Hillege HL, Girbes AR, de Kam PF, Boomsma F *et al.* Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000;**102**:203–10.

15 Hillege HL, van Gilst WH, van Veldhuisen DJ, Navis G *et al.* Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: the CATS randomized trial. *Eur Heart J* 2003;**24**:412–20.

16 Al Suwaidi J, Reddan DN, Williams K, Pieper KS *et al.* Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulation* 2002;**106**:974–80.

17 McCullough PA, Soman SS, Shah SS, Smith ST *et al.* Risks associated with renal dysfunction in patients in the coronary care unit. *J Am Coll Cardiol* 2000;**36**:679–84.

18 Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM *et al.* Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 2002;**137**: 555–62.

19 Wright SR, Reeder GS, Herzog CA, Albright RC *et al.* Acute myocardial infarction and renal dysfunction: a high risk combination. *Ann Intern Med* 2002;**137**:563–70.

20 Shulman NB, Ford CE, Hall WD, Blaufox MD *et al.* Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension* 1989;**13**(5 Suppl):I80–93.

21 Ruilope LM, Salvetti A, Jamerson K, Hansson L *et al.* Renal function and intensive lowering of blood pressure in hypertensive participants of

the hypertension optimal treatment (HOT) study. *J Am Soc Nephrol* 2001;**12**:218–25.

22 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**:886–91.

23 Flack JM, Neaton JD, Daniels B, Esunge P. Ethnicity and renal disease: lessons from the Multiple Risk Factor Intervention Trial and the Treatment of Mild Hypertension Study. *Am J Kidney Dis* 1993; **21**(4 Suppl 1):31–40.

24 Mann JF, Gerstein HC, Pogue J, Lonn E, Yusuf S. Cardiovascular risk in patients with early renal insufficiency. *Am J Cardiovasc Drugs* 2002; **2**:157–62.

25 Maschio G, Alberti D, Janin G, Locatelli F *et al*. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 1996;**334**:939–45.

26 Ruggenenti P, Perna P, Gherardi G, Gaspari F *et al*. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. *Lancet* 1998;**352**:1252–6.

27 Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R *et al*. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;**345**:870–8.

28 Lewis EJ, Hunsicker LG, Clarke WR, Berl T *et al*. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851–60.

29 Ruilope LM, van Veldhuisen DJ, Ritz E, Luscher TF. Renal function: the Cinderella of cardiovascular risk profile. Review. *J Am Coll Cardiol* 2001;**38**:1782–7.