Kidney International, Vol. 68, Supplement 98 (2005), pp. S25–S29

The kidney, a cardiovascular risk marker, and a new target for therapy

DICK DE ZEEUW, HANS L. HILLEGE, and PAUL E. DE JONG

Department of Clinical Pharmacology, Nephrology, and Cardiology, Groningen University Medical Centre, University of Groningen, Groningen, The Netherlands

The kidney, a cardiovascular risk marker, and a new target for therapy. Both reduced filtration power and increased excretion of albumin in the urine are powerful markers for renal and cardiovascular progressive function loss. These risk markers indicate the risk above and beyond the conventional existing risk markers/factors. The risk is substantial, because both reduced filtration and microalbuminuria are highly prevalent in the general population, matching in prevalence with the most well-known risk factor, hypertension.

Therapeutic interventions to preserve renal and cardiovascular function, such as with angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, are highly effective, particularly in those patients that have reduced filtration power. In addition, short-term reduction of albuminuria that follows the renin-angiotensin-aldosterone-system intervention appears to be predictive of long-term cardiovascular and renal protection.

In conclusion, estimated glomerular filtration rate as well as albumin excretion in the urine are powerful predictors for cardiovascular and renal outcome and should be used as such. Intervention and prevention could be aimed at not only at reducing conventional risk markers, but also at reducing albuminuria.

Classic cardiovascular (CV) risk profiling is based on age, gender, blood pressure, cholesterol, smoking, body weight, and type 2 diabetes. The combination of most of these factors renders the doctor the Framingham risk score. This allows us to classify the CV risk of a patient in the office. In addition, it also allows us to initiate and justify our therapeutic strategies. These therapies are aimed at reducing modifiable risk factors and markers, thereby hopefully reducing CV and renal risk. Indeed, there is an intriguing overlap between the kidney and the heart in this respect. Lowering blood pressure has a marked effect on preventing further end-organ damage, both with respect to CV and renal end points. Recently, lowering of cholesterol has been added to this CV and renal protective armamentarium. With respect to diabetes, metabolic control was a big step in preventing the life-threatening end-organ effects of diabetes, which reduces renal as well as CV risk. Reduction of smoking and body weight has also been associated with CV protection, and protective effects on the kidney are suggested.

Despite the armamentarium of risk profilers and related therapies, CV and renal protection remains suboptimal, in that many patients progress to end-stage renal disease or show CV morbidity or mortality despite optimal treatment. Thus, the search for newer, better predictors or, more importantly, new therapy targets, has been ongoing. Aside from parameters reflecting general inflammation (among others, C-reactive protein), an intriguing relation was recently revealed between the kidney and the CV system, which allows novel approaches to CV risk profiling and therapy. Both the level of glomerular filtration rate, as well as the level of albumin leakage in the urine appear to be extremely potent markers for CV and renal disease progression.

The purpose of this short review is to define renal dysfunction as the new risk marker for CV and renal end-organ damage and, more importantly, to mark albuminuria as the novel target for therapy of the 21st century to prevent CV and renal disease progression.

RENAL FILTRATION AS A CV RISK MARKER

Recently, several population surveys established that renal function, measured as estimated glomerular filtration rate (eGFR), varies considerably between individuals, and that unrecognized loss of filtration power and chronic kidney disease (CKD) is relatively common. The estimated prevalence of CKD, defined as an eGFR <60 mL/min, is 6.3% in the United States [1]; when defined as a combination of eGFR <60 or eGFR >60 + microalbuminuria/proteinuria, the estimated prevalence is even higher, 11%. In our town, Groningen, we conducted a survey among the general population and indeed found that the normal value of eGFR is frequently reduced in the normal population (Table 1). Classifying CKD as an eGFR<60, we found close to 8% prevalence and, adding

Key words: kidney, heart, vessels, cardiovascular risk, urinary albumin, renal function, creatinine, renin-angiotensin-aldosterone system.

Table 1. Distribution of renal function (eGFR) in the "general" population in Groningen, The Netherlands, in the PREVEND study (left panel)

eGFR distribution			CKD distribution		
eGFR *mL/min*	N	%	CKD stage	N	%
	8459			8459	
>90	2043	24 (23)	I (>90 + Alb)	225	2.7 (1.3)
60–90	5918	69 (71)	II (60–90 + Alb)	771	9.1 (3.8)
30–60	487	5.7 (5.3)	III (30–60)	487	5.7 (5.3)
15–30	8	0.1 (0.04)	IV (15–30)	8	0.1 (0.04)
<15	3	0.04 (0)	V (<15)	3	0.04 (0)

Abbreviations are: eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease (study); PREVEND, Prevention of Renal and Vascular End-stage Disease; CKD, chronic kidney disease; K/DOQI, Kidney Disease Outcomes Quality Initiative; GFR, glomerular filtration rate; Alb, albumin.

eGFR is estimated with the simplified MDRD formula. CKD is staged according to the K/DOQI guidelines. CKD was defined as a GFR <60 or a GFR >60 + albuminuria >30 mg/24 h (right panel). Because the total PREVEND study population of 8459 patients was enriched for the presence of microalbuminuria, distribution was also calculated in the true random sample from the general population ($N = 2489$). Bold percentages in parentheses are given as those representing the distribution of eGFR and CKD in this unselected population cohort.

the group with an eGFR >60 with microalbuminuria or proteinuria, we found CKD to be present in 12% of the general population (Table 1). Thus, both studies show that CKD has a high prevalence.

Raised levels of serum creatinine or reduced levels of eGFR are associated with increased CV risk, as is found in many different studies and populations. Not only can this be found in already at-risk populations such as in those with heart failure [2] and postmyocardial infarction (Captopril and Thrombolysis Study trial) [3], it is also present in hypertensive or at-risk populations [Heart Outcomes Prevention Evaluation (HOPE)] [4], and even in the general population [Prevention of Renal and Vascular End-stage Disease (PREVEND)] [5]. In all these studies, relatively mild reduction in eGFR (around 60–80 mL/min) was already associated with increased CV risk. Combining the epidemiology of renal function levels in the general population and the CV risk in at-risk populations, one can see that we are dealing with the kidney as a potentially important risk marker of CV disease.

Although the exact mechanism of this relation is not understood, one could hypothesize that decreased renal function is associated with neurohormonal changes (possibly compensating for the reduction in glomerular filtration rate). These hormones, such as angiotensin, may, in turn, cause aggravation of cardiac problems. If true, then angiotensin would be an important target for protecting the kidney and the heart in patients with reduced renal function.

RISK REDUCTION BY TREATMENT OF PATIENTS WITH REDUCED RENAL FUNCTION

There is, unfortunately, no evidence yet that increasing renal function, by, for instance, growing new kidney tissue, will reduce CV or renal risk, which would be an extremely interesting approach. We do have evidence that intervening in the renin-angiotensin-aldosterone system (RAAS) gives CV and renal protection, particularly in those that have reduced renal function. Hillege et al [3] showed that angiotensin-converting enzyme (ACE) inhibition rendered CV protection postmyocardial infarction, more so for those with lower starting eGFR (Fig. 1). Similarly, Mann et al demonstrated that ACE inhibition was at least as cardioprotective in those CV-risk patients that had the lowest eGFR (HOPE) [4]. Also, in patients with more advanced diabetic nephropathy, angiotensin II receptor antagonists show at least as good or even better renal and cardiac protection when eGFR is lower compared with higher [6]. In other words, low glomerular filtration rate may be an excellent CV risk marker, and it also identifies a group of patients that is as good or even better at responding to cardioprotective protection with RAAS intervention strategies.

ALBUMINURIA AS A MARKER OF END-ORGAN DAMAGE

Renal

There is ample evidence that albumin is a good risk marker for renal disease progression. This is seen, in particular, in overt proteinuric patients with nephropathy, as well as in microalbuminuric patients with diabetes. Only recently, Iseki et al had long enough follow-up to relate albuminuria, albeit dipstick measured, to renal outcome in the general population; the higher the albuminuria, the more end-stage renal disease was observed [7]. Recently, Verhave et al showed in the PREVEND study that already slight increases in the level of accurately measured urinary albumin are associated with an increased chance to lose kidney function [8].

Cardiovascular

The evidence for CV risk being associated with albumin leakage in the urine is ample. In the general population, overt albuminuria had been associated with markedly increased CV morbidity and mortality in the Framingham study conducted years ago [9]. More recently, accurate measurements of urine albumin excretion were available, which allowed identification of a CV risk being associated with only slightly increased levels of albumin excretion in the general population in the Danish Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study [10], the PREVEND study [11], and the Nord-Trondelag Health (HUNT) study [12]. Hillege et al also clearly indicated that the relation between albuminuria and CV risk is continuous, even at normal albumin levels (Fig. 2). Also, the hypertensive population shows a similar relation in the MONICA study [13], the HOPE study [14], and the Losartan Intervention For

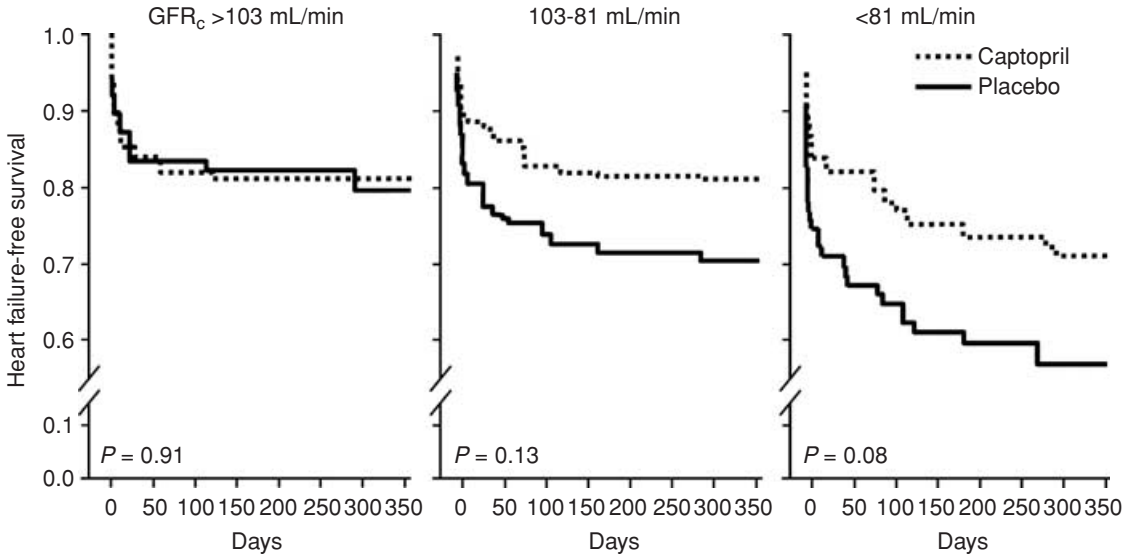

Fig. 1. The effect of ACE-inhibition treatment to protect the heart after myocardial infarction is effective, particularly in those with reduced renal function. Data from [3].

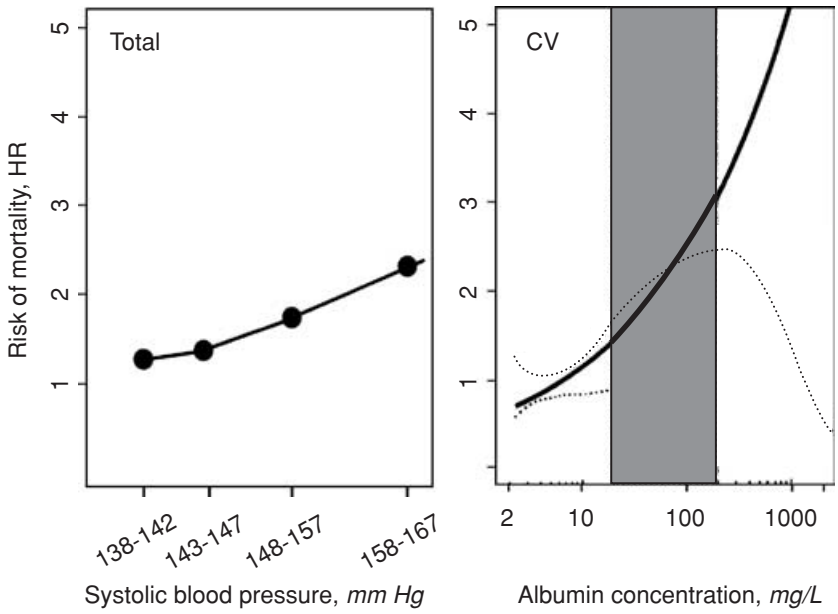

Fig. 2. Blood pressure and albuminuria as predictors of morbidity and mortality. Left panel shows the total mortality data from the Life Insurance data (1.3 million subjects 1925–1939) with increasing systolic blood pressure. Right panel shows the data from the PREVEND study showing CV mortality in relation to baseline albuminuria levels [11].

End Point Reduction in Hypertension (LIFE) study [15]. In diabetes, there is, again, ample evidence of albuminuria as a CV risk predictor following the initial report by Mogensen in 1984 [16].

Thus, there is no doubt that the level of albumin in the urine is an excellent marker both for CV as well as renal risk of patients with existing disease, and even in the general healthy population.

CV AND RENAL PROTECTION BY REDUCING ALBUMINURIA

The most important question that remains is what would happen if we reduce urinary albumin excretion? Would that afford equivalent cardiac and renal protection?

Before answering this question, it is at least intriguing to observe that recent cardiac and renal protective therapies that added to blood pressure lowering, per se, are the introduction of tools to intervene in the RAAS, such as ACE inhibitors and angiotensin II antagonists. These drugs add to CV and renal protection beyond blood pressure control as evidenced, for example, in the IRMA2 [17], REIN [18], IDNT [19], and RENAAL [20] trials for renal endpoints and, for example, in the HOPE [21] and LIFE studies [22] for CV end points.

The fact that these RAAS interventions render such an additive effect has obviously at first been attributed to a reduction of circulating or organ angiotensin II levels or other RAAS parameters. However, both ACEI and angiotensin II antagonists, as well as renin inhibitors, all share a clear antialbuminuric effect beyond their antihypertensive effects. Because albuminuria has been associated with CV and renal risk, one wonders how far the effects on proteinuria explain the organ protection of RAAS inhibition. Even if this relation is not directly causal, one may use albuminuria and its reduction as a marker for effectiveness of therapy.

Indeed, albuminuria reduction has been clearly identified as being predictive for long-term renal outcome in many studies. Recently, de Zeeuw et al analyzed this in the RENAAL trial and showed that initial antialbuminuric effect of treatment is markedly associated with renal protection [23]. In fact, the additive protective effect of the angiotensin II antagonist losartan could be nearly fully explained by its antiproteinuric effect. Similar data were obtained for CV protection: the more medication initially reduced urine albumin excretion, the better the CV system was protected in the long run [24]. Similar renal data were found in Atkins et al in the IDNT trial [25]. Data on less-compromised subjects and patients are still limited. In hypertensive diabetics with microalbuminuria, Parving et al showed that the more you lower albuminuria initially, the better you are protected in the long run against diabetic nephropathy [17]. In the LIFE trial, the data appear to be similar when treating patients with hypertension with left ventricular hypertrophy without selection for albuminuria [26]. Very recent data have been presented by Asselbergs et al out of the PREVEND Intervention Trial, showing that reducing albuminuria with ACE inhibition offers CV protection in healthy volunteers, with only microalbuminuria as entry criterium in the trial [27].

Thus, there are multiple data that link the degree of therapy-induced albuminuria reduction to CV and renal protection. Whether this is solely linked to RAAS intervention or to other albuminuria-reducing therapies remains to be proven in a prospective study.

CONCLUSION

There is ample evidence that risk stratification for end-organ damage should include excreted proteins in the urine (albuminuria) as well as eGFR, next to age, gender, blood pressure levels, cholesterol levels, body weight, smoking, diabetes, and so forth. Given the high residual CV and renal risk under conventional risk-reduction strategies, the enormous impact of albuminuria on patient morbidity and mortality, and the marked predictive value of albuminuria lowering on CV and renal protection, one should use the current drug armamentarium to specifically target albuminuria and reduce it as effectively as possible separate from other risk factors. Because residual albuminuria under effective therapy is as detrimental as without therapy, future efforts should be committed toward more effective proteinuria lowering.

The fact that reduced renal function, be it increased urinary albumin excretion or decreased filtration power, enhances the vulnerability of the CV system for progressive failure, and that renoprotective strategies are directly related to CV protection, suggest that the way to a better heart is through a better kidney. This opens the door for multiorgan disease management and therapy in a disease with multiorgan failure, like type 2 diabetes.

Reprint requests to Prof. Dick de Zeeuw, M.D., Ph.D., Department of Clinical Pharmacology, Groningen University Medical Centre, Ant Deusinglaan 1, 9713 AV Groningen, The Netherlands.
E-mail: d.de.zeeuw@med.rug.nl

REFERENCES

1. Coresh J, Astor BC, Greene T, *et al*: Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 41:1–12, 2003
2. Hillege HL, Girbes AR, de Kam PJ, *et al*: Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 102:203–210, 2000
3. Hillege HL, van Gilst WH, van Veldhuisen DJ, *et al*: CATS randomized trial. Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: The CATS randomized trial. *Eur Heart J* 24:412–420, 2003
4. Mann JF, Gerstein HC, Pogue J, *et al*: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134:629–636, 2001
5. Hillege HL, Verhave JC, Bakker SJL, *et al*: Cystatin-C is superior to creatinine in prediction of mortality in the general population: Data obtained from the PREVEND study. *J Am Soc Nephrol* abstract 2003.
6. Remuzzi G, Ruggenenti P, Perna A, for the RENAAL Study Group, *et al*: Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy: A post hoc analysis of the RENAAL trial results. *J Am Soc Nephrol.* 15:3117–3125, 2004
7. Iseki K, Ikemiya Y, Iseki C, Takishita S: Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 63:1468–1474, 2003
8. Verhave JC, Gansevoort RT, Hillege HL, *et al*: An elevated urinary albumin excretion predicts de novo development of renal function impairment in the general population. *Kidney Int* (Suppl 92):S18–21, 2004
9. Kannel WB, Stampfer MJ, Castelli WP, Verter J: The prognostic significance of proteinuria: The Framingham study. *Am Heart J* 108:1347–1352, 1984
10. Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, *et al*: Urinary albumin excretion. An independent predictor of ischemic heart disease. *Arterioscler Thromb Vasc Biol* 19:1992–1997, 1999
11. Hillege HL, Fidler V, Diercks GF, *et al*: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in the general population. *Circulation* 106:1777–1782, 2002
12. Romundstad S, Holmen J, Kvenild K, *et al*: Microalbuminuria and all-cause mortality in 2,089 apparently healthy individuals: A 4.4–year follow-up study. The Nord-Trøndelag Health Study (HUNT), Norway. *Am J Kidney Dis* 42:466–473, 2003
13. Jensen JS, Feldt-Rasmussen B, Strandgaard S, *et al*: Arterial hypertension, microalbuminuria, and risk of ischemic heart disease. *Hypertension* 35:898–903, 2000
14. Gerstein HC, Mann JF, Yi Q, *et al*; HOPE study investigators. Albuminuria and risk of cardiovascular events, death, and heart

failure in diabetic and nondiabetic individuals. *JAMA* 286:421–426, 2001
15. Wachtell K, Ibsen H, Olsen MH, *et al*: Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: The LIFE study. *Ann Intern Med* 139:901–906, 2003
16. Mogensen CE : Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 310:356–360, 1984
17. Parving H-H, Lehnert H, Brochner-Mortensen J, *et al*, for the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345:870–878, 2001
18. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 349:1857–63, 1997
19. Lewis EJ, Hunsicker LG, Clarke WR, *et al*, for the Collaborative Study Group: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851–860, 2001
20. Brenner BM, Cooper ME, de Zeeuw D, *et al*, for the RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
21. Yusuf S, Sleight P, Pogue J, *et al*: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 342:145–153, 2000
22. Dahlöf B, Devereux RB, Kjeldsen SE, *et al*, for the LIFE study group: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet* 359:995–1003, 2002
23. De Zeeuw D, Remuzzi G, Parving H-H, *et al*: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. *Kidney Int* 65:2309–2320, 2004
24. De Zeeuw D, Remuzzi G, Parving H-H, *et al*: Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 110:921–927, 2004
25. Atkins RC, Briganti FM, Lewis JB, *et al*: Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. *Am J Kidney Dis* 45:281–287, 2005
26. Ibsen H, Olsen MH, Wachtell K, *et al*: Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: Losartan intervention for endpoint reduction in hypertension study. *Hypertension* 45:198–202, 2005
27. Asselbergs FW, Diercks FH, Hillege HL, *et al*: Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuric. *Circulation* 110:2809–2816, 2004