Kidney International, Vol. 66, Supplement 92 (2004), pp. S45–S49

Effect of proteinuria and glomerular filtration rate on cardiovascular risk in essential hypertension

JULIAN SEGURA, CARLOS CAMPO, and LUIS M. RUILOPE

Unidad de Hipertensión Arterial, Hospital 12 de Octubre, Madrid, Spain

Effect of proteinuria and glomerular filtration rate on cardiovascular risk in essential hypertension. Changes in renal function related with essential hypertension are associated with an elevated cardiovascular morbidity and mortality. Indices of altered renal function (e.g., microalbuminuria, increased serum creatinine concentrations, decrease in estimated creatinine clearance or GFR, and overt proteinuria) are independent predictors of cardiovascular morbidity and mortality. The Framingham Heart Study documented the relevance of proteinuria for cardiovascular prognosis in the community. The INSIGHT Study assessed the role of proteinuria as a risk factor in essential hypertension. The presence of proteinuria at baseline turned out to be a very potent predictor for the development of cardiovascular events and death in patients with essential hypertension and one or more associated cardiovascular risk factors. Recent data indicate that minor derangements of renal function, including proteinuria, are associated, both in the community and in the hypertensive population, with the clustering of cardiovascular risk factors observed in metabolic syndrome that promote progression of atherosclerosis. Renal function has to be routinely evaluated in every hypertensive patient, and the presence of minor alterations considered in the stratification of cardiovascular risk in hypertensive patients.

Evidence is accumulating that the kidney is not only a target of the hypertensive process, but also contributes to the development of cardiac and cerebral complications. Although in the laboratory, subtle changes in renal function may be detected by measuring renal blood flow or glomerular filtration rate (GFR), the practicing clinician must rely on the determination of serum creatinine, creatinine clearance, and urinary albumin or protein excretion. Several studies have shown that in essential hypertension the presence of small amounts of albumin in the urine (microalbuminuria) is an independent risk factor for future cardiovascular events [1]. Recent data indicate that also serum creatinine acts as a marker of risk [2, 3]. Interestingly, the predictive power of serum creatinine is independent from the finding of micro- or macroalbuminuria and demonstrable already with relatively normal values of this substance [3, 4]. Last year the Seventh Report of the Joint National Committee (JNC-7) [5] recognized microalbuminuria and an estimated GFR below 60 mL/min/1.73m^2 as major cardiovascular risk factors. The European Society of Hypertension-European Society of Cardiology (ESH-ESC) guidelines for the management of arterial hypertension consider slight increase in serum creatinine (1.3–1.5 mg/dL in men, 1.2–1.4 mg/dL in women) and microalbuminuria as target organ damage, and higher values of serum creatinine or the presence of proteinuria as associated clinical conditions [6]. These guidelines recommend measurement of serum creatinine and estimation of GFR as routine tests in hypertensive patients, and they also recommend the estimation of albuminuria [5, 6].

Key words: albuminuria, glomerular filtration rate, cardiovascular risk.

Diagnosis of renal damage in clinical practice

The diagnosis of renal dysfunction in patients with different forms of cardiovascular disease is based on two findings (i.e., elevated serum creatinine or a decrease in GFR) usually determined as estimated GFR or creatinine clearance [7, 8], and/or the detection of an elevated urinary excretion of albumin below (microalbuminuria, 30–300 mg/day) or above (macroalbuminuria, >300 mg/day) the usual laboratory methods to detect proteinuria. Chronic kidney disease (CKD) has recently been defined as serum creatinine values above 1.5 mg/dL (132 μmol/L) in men and 1.4 mg/dL (123 μmol/L) in women [9], or by the finding of estimated GFR below 60 mL/min [2, 9]. While an elevated serum creatinine concentration points to a reduced rate of glomerular filtration, an increased rate of albumin or protein excretion points to a derangement in the glomerular filtration barrier [10]. Microalbuminuria has been shown to correlate with the presence of nephrosclerosis [11], while the presence of proteinuria generally indicates the existence of established renal parenchymatous damage [10]. On the other hand, the finding of a serum creatinine value within the normal range can be accompanied by a diminished GFR value, particularly in elderly patients [12]. The presence of a diminished renal function is more prevalent

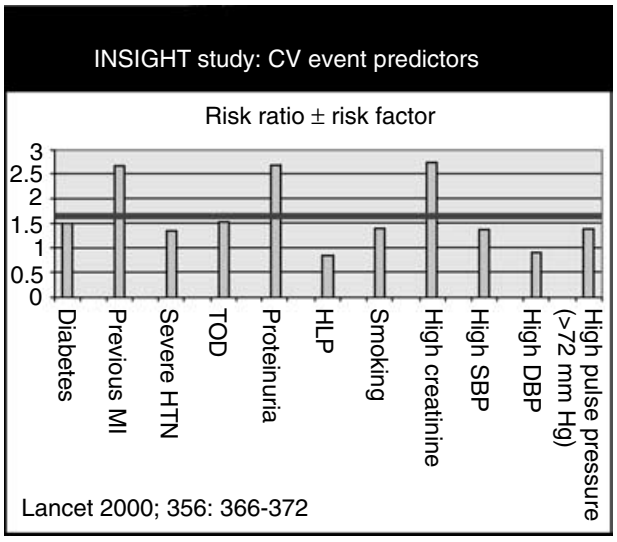

Fig. 1. INSIGHT study showed that proteinuria is a very powerful cardiovascular risk predictor, as an elevated serum creatinine or the existence of a previous myocardial infarction. Abbreviations: MI, myocardial infarction; HTN, hypertension; TOD, target organ damage; HLP, hyperlipidemia; SBP, systolic blood pressure; DBP, diastolic blood pressure.

that previously thought in essential hypertension. This is particularly so if estimated creatinine clearance is considered routinely in the evaluation of all hypertensive patients [13].

Proteinuria and microalbuminuria as predictors of cardiovascular risk

The relevance of proteinuria for CV prognosis in the community was documented by the Framingham Heart Study [14]. The presence of proteinuria in patients with treated essential hypertension varies between 4% and 16% in different series of treated hypertensive patients [15]. As in subjects with diabetic nephropathy, the presence of albuminuria or proteinuria in nondiabetic subjects is independently associated with an increased CV risk in longitudinal studies [3, 16–24]. The INSIGHT study (International Nifedipine GITS study: Intervention as a goal in Hypertension Treatment) compared the capacity of a long-acting dihydropiridine and a diuretic to diminish cardiovascular events and death in essential hypertension [25]. This study assessed the role of proteinuria as an independent cardiovascular risk factor. The analysis of the data revealed that proteinuria conferred a very powerful risk similar to that accompanying an elevated serum creatinine or the existence of a previous myocardial infarction (Fig. 1).

Attention has recently been drawn to microalbuminuria and its relevance as a predictor of cardiovascular disease [26]. Its prevalence varies between 20% and 30% of untreated patients and up to 25% in treated patients. Very recently, it has been shown that the presence of microalbuminuria in primary hypertension is associated to an elevated CV risk [10, 27]. The risk is similar to the one accompanying existing coronary artery disease. According to a persuasive hypothesis, microalbuminuria constitutes the renal expression of a generalized disorder characterized by increased endothelial permeability [28–31], abnormalities of the fibrinolytic and coagulation pathways, and activation of inflammatory process [32]. This hypothesis provides an explanation for the link between increased urinary albumin excretion (UAE) and elevated cardiovascular risk [26]. Some preliminary data indicate that in primary hypertension, microalbuminuria is also a predictor of progressive deterioration of renal function in primary hypertension [33, 34]. In the majority of the published studies involving hypertensive patients, microalbuminuria was defined as a UAE between 30 and 300 mg/day. As used in the LIFE Study [35], a simpler alternative is the measurement of the albumin:creatinine ratio in single morning first-void urine specimen (>3.5 mg/albumin/mmol creatinine) for the diagnosis of microalbuminuria. In patients with moderately severe hypertension, this recent study showed that left ventricular hypertrophy (LVH) is associated with increased prevalences of micro- and macroalbuminuria compared with patients without LVH [35]. Furthermore, in the HOPE study [16], the relative risk of the primary end point in the fourth quartile was 1.97 (albumin:creatinine ratio >1.62 mg/mmol) compared with the lowest quartile of albumin:creatinine ratio. For every 0.4 mg/mmol increase in albumin:creatinine ratio level, the adjusted hazard of major cardiovascular events increases by 5.9% [16]. As the data accumulate from the ongoing trials, and the normal range for urinary albumin excretion in hypertension is better defined, the measurement of UAE rates may serve a dual purpose. First, the presence of albuminuria is a powerful way to identify those patients requiring an integrated intervention on multiple cardiovascular risk factors. Second, a failure to regress albumin excretion in urine may indicate an inadequacy of that intervention [36]. In this sense, Mann et al [37] have described that in people at high cardiovascular risk, microalbuminuria predicts the development of clinical proteinuria in nondiabetic and in diabetic people. Progression of albuminuria was found in one of five participants in the 4.5-year of follow-up in the HOPE trial. The progression was seen in one of three patients with diabetes and in one of seven without diabetes. This progression was effectively reduced was reduced by ACE inhibition in the subgroups with and without diabetes.

Correlation of proteinuria and glomerular filtration rate with cardiovascular risk

Both proteinuria and GFR are independent predictors of CV morbidity and mortality. Reduced GFR is associated with a high prevalence of CV risk factors and a higher prevalence of CV disease. Several studies across a broad

Table 1. Cardiovascular risk factors or markers associated to a mild decrease in estimated GFR (for review see [54])

Disturbed lipoprotein(a) concentrations
Insulin resistance and impaired glucose tolerance
Increased oxidate stress
Increment in pulse wave velocity
Increased serum uric acid levels
Sympathetic overactivity
Accumulation of ADMA
Inflammatory and procoagulant biomarkers (CRP, fibrinogen, interleukin 6, factor VIIc, factor VIIIc, plasmin-antiplasmin complex, and D-dimer)
Obesity and body fat distribution
Non-dipping pattern of ambulatory blood pressure

ADMA, asymmetric dimethylarginine; CRP, C-reactive protein.

spectrum of populations, such as the HOPE study [16], the Cardiovascular Health Study (CHS) [38], the Hypertension Optimal Treatment (HOT) Study [2], the Framingham and Framingham Offspring Studies [14, 39], and the Atherosclerosis Risk in Communities (ARIC) study [40], have shown that levels of systolic blood pressure, total cholesterol, and the percentage of patients with low HDL cholesterol are greater in subjects with decreased GFR. Moreover, the percentages of subjects with diabetes, LVH, ischemic heart disease, and heart failure are higher in those with decreased GFR [2, 14, 41–43]. Mild degrees of renal failure have been shown to be associated to a series of risk factors or markers that are summarized in Table 1. A similar clustering of risk factors has been reported in microalbuminuric subjects, in particular, those linked to insulin resistance [44–48].

Reduced GFR is also associated with clinical CV outcome in prospective studies. In high-risk populations, most studies have suggested that decreased GFR is an independent risk factor for outcomes. This is true in the elderly, in whom even mild reductions of kidney function are associated with worse outcomes [38], in studies of hypertensive subjects [49], in hypertensive patients with baseline normal renal function and development of hypertensive nephrosclerosis during their follow-up [50], in population studies with higher than normal prevalence of diabetes [50], and among older patients undergoing general surgery [52]. In low-risk populations or community-based studies, the relationship between the level of kidney function and outcomes has not been as clear. Discrepancies in the studies include differences in the study populations, and alternate measures of kidney function, considering that serum creatinine is less sensitive than estimated GFR to detect small differences in level of kidney function [13]. In any case, the association of reduced GFR and CV risk is supported by evidence showing the relationship between reduced GFR and nontraditional CV risk factors that frequently are not assessed [53]. Reduced GFR may then be a marker of undiagnosed vascular disease, or alternatively, a marker for the severity of diagnosed vascular disease [54]. Moreover, recent data have suggested that patients with reduced GFR are less likely to receive medications or therapies, such as angiotensin-converting enzyme inhibitors, beta-blockers, aspirin, platelet inhibitors, thrombolytics, or percutaneous intervention than patients with preserved GFR [55–57].

Table 2. Prevalence of microalbuminuria and proteinuria according to estimated glomerular filtration rate (GFR)

Estimated GFR (mL/min/1.73m^2)	*N* (%)	Microalbuminuria %	Proteinuria %
>90	680 (65)	31.9	3.5
60–90	240 (23)	30.2	5.0
<60	127 (12)	37.6	10.2
Total	1047	31.3	4.7

Definitely, both proteinuria and reduced GFR are associated with an increased CV risk. Nevertheless, it is not well established the percentage of patients presenting both disturbances. We have analyzed the prevalence of microalbuminuria and proteinuria according to GFR values in a cohort of 1047 essential hypertensive patients attended in a hospital located hypertension unit. As can be seen in Table 2, the prevalences of microalbuminuria and proteinuria increase significantly at estimated GFR values below 60 mL/min/1.73m^2. Both microalbuminuria and proteinuria were significantly associated with lower values of estimated GFR, diabetes mellitus, male gender, age above 60 years, and the presence of target organ damage or associated clinical conditions. These findings contribute to explain the exponential increase in CV risk observed with progressive decay in renal function.

Microalbuminuria could be present in hypertensive patients with preserved GFR, including those presenting hyperfiltration as an early marker of renal dysfunction. Urinary albumin excretion would increase progressively in association with an increased severity of hypertension and with the progressive decay in GFR values, as can be seen in Figure 2.

Simultaneous correction or prevention of renal and cardiovascular damage is required

Table 3 summarizes the therapeutic attitudes that must be considered in presence of CKD. They contemplate the simultaneous performance of cardiovascular and renal protection. Lifestyle changes, with particular emphasis on diminishing salt intake, avoiding obesity, and refraining from smoking are very important. Strict blood pressure control (probably below 125/75 mm Hg in every patient) is required, and the administration of a combination of drugs needed [5, 6]. The presence of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker is required because blockade of angiotensin II effects has demonstrated to improve the long-term renal outcome of patients with nephrosclerosis [58, 59]. The role of dual blockade of renin-angiotensin system combining an angiotensin-converting enzyme inhibitor

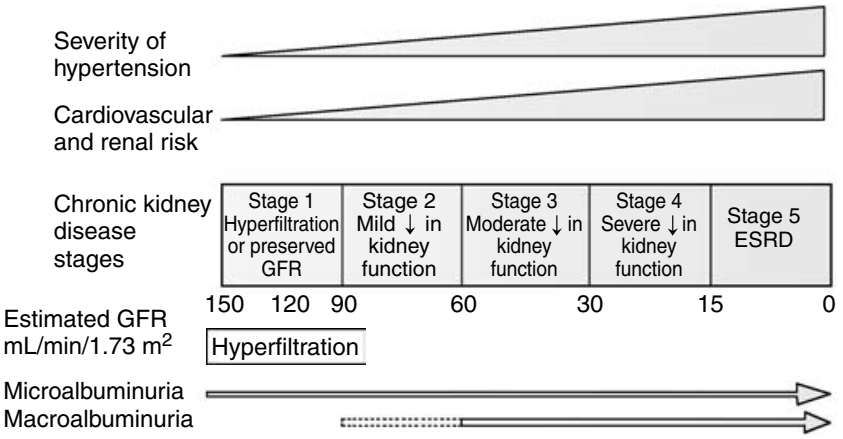

Fig. 2. Relationship among severity of hypertension, cardiovascular and renal risk, and the presence of chronic kidney disease and increased urinary albumin excretion.

Table 3. Therapeutic attitudes in patients with chronic kidney disease and hypertension

Lifestyle changes
(Salt intake, body weight, and stop smoking)
Strict blood pressure control
(<125/75 mm Hg): Combination therapy required in most cases.
ACE inhibitor or ARB is required
Control of associated risk factors
Lipids: statins, fibrates
Insulin resistance: insulin sensitizers (metformin, glitazones?)
Platelet aggregation: aspirins, others?

and an angiotensin receptor blocker remains to be elucidated in essential hypertensive patients, albeit it has demonstrated its efficacy in primary renal disease accompanied by proteinuria [60].

The presence of CKD, manifested as albuminuria and/or reduced GFR, appears to be an independent CV risk factor, particularly in higher-risk populations. According to the National Kidney Foundation task force recommendation, patients with CKD should be considered in the highest risk group for CV events [9]. The JNC-7 includes CKD as a "compelling" indication, justifying lower target blood pressure and treatment with specific antihypertensive agents [5]. Similarly, the recently published "NKF-K/DOQI Clinical Practice Guidelines on Managing Dyslipidemia in Chronic Kidney Disease" recommend that all patients with CKD be included in the highest risk group, justifying a lower target low-density lipoprotein cholesterol level [61]. The American Heart Association suggests that the routine evaluation of patients with CV disease, or those at high CV risk, should include measurement of spot urine albumin-to-creatinine ratio or total protein-to-creatinine ratio and estimation of GFR by serum creatinine and prediction equations [54].

Reprint requests to Luis M. Ruilope, Unidad de Hipertensión Arterial, Hospital 12 de Octubre, Madrid, Spain.
E-mail: ruilope@ad-hocbox.com

REFERENCES

1. Rosa TT, Palatini P: Clinical value of microalbuminuria in hypertension. *J Hypertens* 18:645–654, 2000
2. Ruilope LM, Salvetti A, Jamerson K, *et al*: Renal function and intensive lowering of blood pressure in hypertensive participants of the Hypertension Optimal Treatment (HOT) study. *J Am Soc Nephrol* 12:218–225, 2001
3. 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* 13:2213–2222, 2002
4. Schillaci G, Reboldi G, Verdecchia P: High-normal serum creatinine concentration is a predictor of cardiovascular risk in essential hypertension. *Arch Intern Med* 161:886–891, 2001
5. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 289:2560–2572, 2003
6. Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology Guidelines for the management of Arterial Hypertension. *J Hypertens* 21:1011–1054, 2003
7. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
8. Levey AS, Bosch JP, Lewis JB, *et al*: A more accurate method to estimate glomerular rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130:461–470, 1999
9. National Kidney Foundation: Clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. Definition and classification of stages of chronic kidney disease. *Am J Kidney Dis* 39(Suppl 1):S46–S75, 2002
10. Ruilope LM, Rodicio JL: Clinical relevance of proteinuria and microalbuminuria. *Curr Opin Nephrol Hypertens* 2:962–967, 1993
11. Minram A, Ribstein J, DuCalair G: Is microalbuminuria a marker of early intrarenal vascular dysfunction in essential hypertension? *Hypertension* 23:1018–1021, 1994
12. Lindeman R, Tobin J, Shock NW: Longitudinal studies on the rate of decline in renal function with age. *J Am Geriat Soc* 33:278–285, 1985
13. Segura J, Campo C, Rodicio JL, Ruilope LM: How relevant and frequent is the presence of mild renal insufficiency in essential hypertension? *J Clin Hypertens* 4:332–336, 2002
14. Culleton BF, Larson MG, Wilson PWF, *et al*: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 56:2214–2219, 1999
15. Samuelsson O, Wilhelmsen L, Elmfeldt D, *et al*: Predictors of cardiovascular morbidity in treated hypertension: Results from the primary preventive trial in Goteborg, Sweden. *J Hypertens* 3:167–176, 1985
16. Gerstein HC, Mann JF, Yi Q, *et al*: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286:421–426, 2001
17. Agewall S, Wikstrand J, Ljungman S, *et al*: Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. Risk Factor Intervention Study Group. *Am J Cardiol* 80:164–169, 2001
18. Miettinen H, Haffner SM, Lehto S, *et al*: Proteinuria predicts

stroke and other atherosclerotic vascular disease events in nondiabetic and non–insulin-dependent diabetic subjects. *Stroke* 27:2033–2039, 1996
19. Culleton BF, Larson MG, Parfrey PS, *et al*: Proteinuria as a risk factor for cardiovascular disease and mortality in older people: A prospective study. *Am J Med* 109:1–8, 2000
20. Grimm RJ, Svendsen K, Kasiske B, *et al*: Proteinuria is a risk factor for mortality over 10 years of follow-up. MRFIT Research Group: Multiple Risk Factor Intervention Trial. *Kidney Int* 63:S10–S14, 1997
21. Ljungman S, Wikstrand J, Hartford M, *et al*: Urinary albumin excretion—A predictor of risk of cardiovascular disease. A prospective 10-year follow-up of middle-aged nondiabetic normal and hypertensive men. *Am J Hypertens* 9:770–778, 1996
22. Hillege HL, Fidler V, Diercks GF, *et al*: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 106:1777–1782, 2002
23. Jager A, Kostense PJ, Ruhe HG, *et al*: Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: Five-year follow-up of the Hoorn Study. *Arterioscler Thromb Vasc Biol* 19:617–624, 1999
24. Kannel WB, Stampfer MJ, Castelli WP, *et al*: The prognostic significance of proteinuria: The Framingham study. *Am Heart J* 108:1347–1352, 1984
25. Brown MJ, Palmer CR, Castaigne A, *et al*: Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a goal in Hypertension Treatment (INSIGHT). *Lancet* 356:366–372, 2000
26. Agrawal B, Berger A, Wolf K, Luft FC: Microalbuminuria screening by reagent strip predicts cardiovascular risk in hypertension. *J Hypertens* 14:223–228, 1996
27. Campese VM, Bianchi S, Bigazzi R: Is microalbuminuria a predictor of cardiovascular and renal disease in patients with essential hypertension? *Curr Opin Nephrol Hypertens* 9:143–147, 2000
28. Pedrinelli R, Dell'Omo G, Penno G, *et al*: Non-diabetic microalbuminuria, endothelial dysfunction and cardiovascular disease. *Vasc Med* 6:257–264, 2001
29. Clausen P, Feldt-Rasmussen B, Jensen G, *et al*: Endothelial haemostatic factors are associated with progression of urinary albumin excretion in clinically healthy subjects: A 4-year prospective study. *Clin Sci* 97:37–43, 1999
30. Jensen JS: Renal and systemic transvascular albumin leakage in severe atherosclerosis. *Arterioscler Thromb Vasc Biol* 15:1324–1329, 1995
31. Clausen P, Jensen JS, Jensen G, *et al*: Elevated urinary albumin excretion is associated with impaired arterial dilatory capacity in clinically healthy subjects. *Circulation* 103:1869–1874, 2001
32. Paisley KE, Beaman M, Tooke JE, *et al*: Endothelial dysfunction and inflammation in asymptomatic proteinuria. *Kidney Int* 63:624–633, 2003
33. Ruilope LM, Campo C, Rodriguez-Artalejo F, *et al*: Blood pressure and renal function therapeutic implications. *J Hypertens* 14:1259–1263, 1996
34. Pinto-Siestma SJ, Janssen WM, Hillege HL, *et al*: Urinary albumin excretion is associated with renal function abnormalities in a nondiabetic population. *J Am Soc Nephrol* 11:1882–1888, 2000
35. Watchell K, Olsen MH, Dahlof B, *et al*: Microalbuminuria in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE study. *J Hypertens* 20:405–412, 2002
36. Redon J, Williams B: Microalbuminuria in essential hypertension: Redefining the threshold. *J Hypertens* 20:353–355, 2002
37. Mann JFE, Gerstein HC, Yi QL, *et al*: Development of renal disease in people at high cardiovascular risk: Results of the HOPE randomized study. *J Am Soc Nephrol* 14:641–647, 2003
38. Manjunath G, Tighiouart H, Coresh J, *et al*: Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int* 63:1121–1129, 2003
39. Jacques PF, Bostom AG, Wilson PW, *et al*: Determinants of plasma total homocysteine concentration in the Framingham Offspring cohort. *Am J Clin Nutr* 73:613–621, 2001
40. Perneger TV, Nieto FJ, Whelton PK, *et al*: A prospective study of blood pressure and serum creatinine. Results from the 'Clue' Study and the ARIC Study. *JAMA* 269:488–493, 1993
41. 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
42. Manjunath G, Tighiouart H, Ibrahim H, *et al*: Level of kidney function as a risk factor for atherosclerotic cardiovascular disease in the community. *J Am Coll Cardiol* 41:47–55, 2003
43. Shlipak MG, Fried LF, Crump C, *et al*: Cardiovascular disease risk status in elderly persons with renal insufficiency. *Kidney Int* 62: 997–1004, 2002
44. Pedrinelli R, Dell'Omo G, Di Bello V, *et al*: Microalbuminuria, an integrated marker of cardiovascular risk in essential hypertension. *J Hum Hypertens* 16:79–89, 2002
45. de la Sierra A, Bragulat E, Sierra C, *et al*: Microalbuminuria in essential hypertension: Clinical and biochemical profile. *J Biomed Sci* 57:287–291, 2000
46. Leoncini G, Sacchi G, Viazzi F, *et al*: Microalbuminuria identifies overall cardiovascular risk in essential hypertension: An artificial neural network-based approach. *J Hypertens* 20:1315–1321, 2002
47. Sowers JR, Haffner S: Treatment of cardiovascular and renal risk factors in the diabetic hypertensive. *Hypertension* 40:781–788, 2002
48. Dell'Omo G, Penno G, Giorgi D, *et al*: Association between high-normal albuminuria and risk factores for cardiovascular and renal disease in essential hypertensive men. *Am J Kidney Dis* 40:1–8, 2002
49. Shulman NB, Ford CE, Hall WD, *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* 13(Suppl 5):I80–I93, 1989
50. Segura J, Campo C, Gil P, *et al*: Development of chronic kidney disease and cardiovascular prognosis in essential hypertensive patients. *J Am Soc Nephrol* 15:1616–1622, 2004
51. Henry RM, Kostense PJ, Bos G, *et al*: Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn study. *Kidney Int* 62:1402–1407, 2002
52. O'Brien MM, Gonzales R, Shroyer AL, *et al*: Modest serum creatinine elevation affects adverse outcome after general surgery. *Kidney Int* 62:585–592, 2002
53. Shlipak MG, Fried LF, Crump C, *et al*: Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 107:87–92, 2003
54. Sarnak MJ, Levey AS, Schoolwerth AC, *et al*: Kidney disease as a risk factor for development of cardiovascular disease. A statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108:2154–2169, 2003
55. Shlipak MG, Heidenreich PA, Noguchi H, *et al*: Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 137:555–562, 2002
56. Wright RS, Reeder GS, Herzog CA, *et al*: Acute myocardial infarction and renal dysfunction: A high-risk combination. *Ann Intern Med* 137:563–570, 2002
57. McCullough PA, Sandberg KR, Borzak S, *et al*: Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. *Am Heart J* 144:226–232, 2002
58. Wright JT, Jr., Bakris G, Greene T, *et al*, for the African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 288:2421–2431, 2002
59. Segura J, Campo C, Rodicio JL, Ruilope LM: ACE inhibitors and appearance of renal events in hypertensive nephrosclerosis. *Hypertension* 38:645–649, 2001
60. Nakao N, Yoshimura A, Morita H, *et al*: Combination treatment of angiotensin II-receptor blocker and angiotensin-converting enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. *Lancet* 361:117–124, 2003
61. National Kidney Foundation: K/DOQI clinical practice guidelines on managing dyslipidemias in chronic kidney disease. *Am J Kidney Dis* 41(Suppl 3):S1–S77, 2003