Chronic Kidney Disease as a Situation of High Added Risk in Hypertensive Patients

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Recent guidelines for the management of hypertension have recognized the relevance of renal function on cardiovascular prognosis of hypertensive patients. In fact, growing evidences have confirmed that as soon as renal function exhibits minor derangements, cardiovascular risk starts a continuous rise until the development of end-stage renal disease. Both estimated glomerular filtration rate and urinary albumin excretion are associated with an increased incidence of cardiovascular events and death among hypertensive patients and in general population. Consequently, hypertensive patients presenting with chronic kidney disease are considered by guidelines as high-risk patients, and strict blood pressure control should be considered as a part of an integrative therapeutic approach, including correction of anemia, treatment of dyslipidemia, cessation of tobacco use, and antiplatelet therapy. This paper briefly reviews the most recent evidences about pharmacologic therapies in high-risk patients, focusing on benefits related to improvement of cardiovascular risk factors in hypertensive patients with chronic kidney disease.

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Recently, the Seventh Report of the Joint National Committee (JNC-7) has recognized microalbuminuria and an estimated GFR (eGFR) value <60 ml/min per 1.73 m^2 as two major cardiovascular risk factors (CVRF) (1). In the same line, the Guidelines of the European Society of Hypertension–European Society of Cardiology (ESH-ESC) (2) define the existence of a high added risk in hypertensive patients by the presence of a given level of BP accompanied or not by the presence of associated CVRF, target organ damage (TOD), diabetes, or associated clinical conditions (ACC). These guidelines consider slight increase in serum creatinine (1.3 to 1.5 mg/dl in men, 1.2 to 1.4 mg/dl in women) and microalbuminuria as TOD, and higher values of serum creatinine or the presence of proteinuria as ACC (2). The presence of very elevated BP levels is required in the absence of other CVRF to consider that a patient has a high added CV risk, whereas only high-normal BP levels or even lower values are required for the same recognition when the patient presents with three or more associated CVRF, TOD, diabetes, or ACC. According to this, hypertensive patients with a high-added level of CV risk can be found in any of the three stages of the CV and renal continuum (Figure 1). Since the publication of the guidelines, growing evidence has been added to confirm that as soon as renal function exhibits minor derangements, CV risk starts a continuous rise until the development of ESRD (3,4).

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Chronic Kidney Disease in the General Population and in High-Risk Subgroups

The presence of chronic kidney disease (CKD) relies on the determination of serum creatinine, creatinine clearance, and/or urinary albumin excretion (UAE). The Framingham Heart Study showed a relevant prevalence of mild renal insufficiency in the general population, on the basis of serum creatinine values (8.7% in men and 8.0% in women) (5). The prevalence of a mild decrease in renal function in the community could be even higher according to the values of estimated creatinine clearance seen in the Third National Health and Nutrition Examination Survey (6,7). Among patients who were referred to our hypertension unit, 7.6% have a decreased renal function according to serum creatinine levels, and one of every four patients has a decreased creatinine clearance (8).

Recently, community-based longitudinal studies have demonstrated that CKD is an independent risk factor for the composite study outcome, including myocardial infarction, fatal coronary heart disease, stroke, and death (9). These results were confirmed recently in a Japanese population (10) and in a population with preexisting CV disease (11). In essential hypertensive patients with normal renal function (defined as eGFR >90 ml/min per 1.73 m^2), those who developed CKD during 13 yr of follow-up presented a rate of CV events 2.5 times higher than those with preserved renal function (12).

Microalbuminuria is associated with an increased incidence of CV events and death, as well as with all-cause mortality. Initial evidence came from observations involving high-risk patients (13–15). The data from the HOPE study (16) came to confirm the predictive value of microalbuminuria that attained a predictive capacity similar to that of previous coronary artery disease and was equal for patients with and without accompanying diabetes. The relevance of UAE as a CVRF in hypertensive patients without diabetes (13,17–19) and in the general

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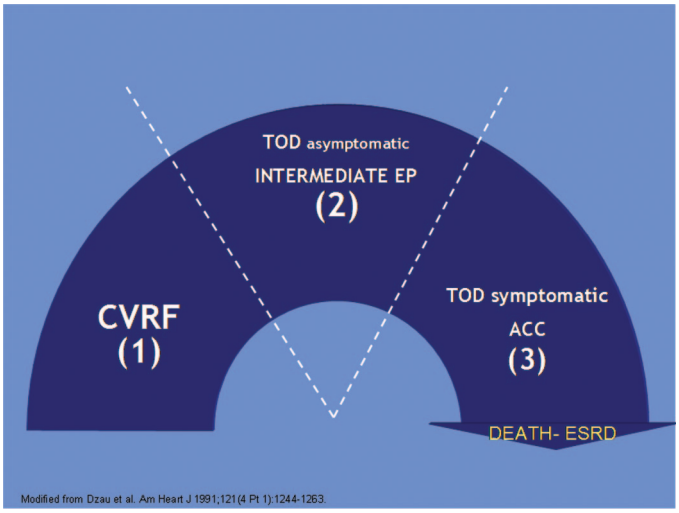

Figure 1. Progression of cardiovascular and renal disease. CVRF, cardiovascular risk factors; TOD, target organ damage; ACC, associated clinical conditions.

population (20,21) also has been demonstrated. Some of these studies (16,21) have described that the relationship between urinary albumin and CV risk is a continuum that starts below the cutoff point of 30 mg/d albumin (or 30 mg/g creatinine) that normally allows the classification of a given patient as having microalbuminuria. This fact has led to questioning whether the actual threshold to define a normal value of this parameter is adequate (22).

Definitely, both UAE and reduced GFR are associated with an increased CV risk. Nevertheless, the percentage of patients who present both disturbances is not well established. We have analyzed the prevalence of microalbuminuria and proteinuria according GFR values in a cohort of 1047 essential hypertensive patients who attended our hospital-located hypertension unit. As can be seen in Table 1, the prevalences of microalbuminuria and proteinuria increase significantly at eGFR values <60 ml/min per 1.73 m^2. Both microalbuminuria and proteinuria were significantly associated with lower values of eGFR, diabetes (42.4%), male gender (36.4%), age above 60 yr (33.2%), and the presence of TOD or ACC (39.6%). These findings contribute to explain the exponential increase in CV risk that was observed with progressive decay in renal function (23). Moreover, CKD could appear together with other TOD as left ventricular hypertrophy (LVH). In fact, the fall in GFR in hypertensive patients is particularly accelerated when the elevated BP is accompanied by the concentric pattern of LVH (24). Concentric LVH is a strong marker of the severity of hypertension (25), and it could be an indicator that CV and renal damages are closely related.

Table 1. Prevalences of microalbuminuria and proteinuria according to estimated GFR values[a]

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

[a]GFR, glomerular filtration rate.

Pharmacologic Therapy in High-Risk Hypertensive Patients

Results from big trials in hypertensive patients show that controlling BP is the most important issue (26). However, there is general agreement in considering that patients with a high-added CV risk require antihypertensive therapy to lead BP to the expected goal of control, which is <130/80 mmHg in most cases. This BP goal must be attained in patients with ACC or any degree of renal damage and also in patients with diabetes (2). The presence of other forms of TOD and/or three or more associated CVRF require that BP levels be maintained at levels <140/90 mmHg.

All of the recently published trials in arterial hypertension have been reviewed in the Trialists Meta-analysis (27). Data contained in this meta-analysis refer most importantly to the comparison of active therapy and placebo and of lower and higher BP goal and to the comparison between different antihypertensive drug classes. All of these comparative data have been constructed by the comparison of the time elapsed until the development of one event or death in the required number of patients according to the initial sample size calculation. Practically, it can be considered that the great majority of the events and death considered in this meta-analysis took place in patients with high-added CV risk, for whom the greatest likelihood for CV morbidity and mortality was present. The main conclusion of this meta-analysis is that it is attainment of BP control and not the type of therapy used that matters when antihypertensive therapy is concerned. It is true that the class of the angiotensin receptor blocker showed positive differences when compared with other therapies, in particular diuretics and β blockers. However, data from the VALUE trial (28) were not included. This fact is relevant also for the analysis of the calcium channel blockers as will be the inclusion of the INVEST, MOSES, ACTION, and CAMELOT trials (29–32). Considering these new trials, recent analysis suggests that antihypertensive drug treatment improves outcome mainly through lowering of systolic BP (33).

Treatment of Patients with CKD

In addition to antihypertensive therapies, recent evidence seems to indicate that a statin must be included in the treatment of a relevant percentage of high-risk hypertensive patients, at least in patients with diabetes in any of the three stages and in all of those in stage 3 (34,35). Once BP control is attained, antiplatelet therapy with aspirin must be contemplated at least in patients at stage 3 (36). These added therapies could contribute to bias the effect of a given antihypertensive therapy (whether monotherapy or a combination). Statins have proved to be of great value in patients with an elevated global CV risk accompanied or not by elevated LDL cholesterol levels (37). Moreover, the overall clinical benefits that are observed with statin therapy seem to be greater than what might be expected

from changes in lipid profile alone, suggesting that the beneficial effects of statins may extend beyond their effects on serum cholesterol levels. In fact, much evidence has shown the pleiotropic effects of statins in improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, and decreasing oxidative stress and vascular inflammation (38). Recent data from the Brisighella Heart Study demonstrated that the use of lipid-lowering measures could significantly improve BP control in patients with both hypercholesterolemia and hypertension, enhancing the reduction in BP in patients who are treated with statins (39).

Patients who present with CKD experience higher mortality and adverse CV event rates, which remains significant after adjustment for conventional CVRF (40). Moreover, CKD is common in patients with heart failure and coronary artery disease, and these patients have more advanced atherosclerosis (41,42). Nevertheless, there is a lack of appropriate risk factor modification and intervention, despite established awareness of their high CV risk and the evidence of better outcomes if they receive adequate therapy (40,41,43). In fact, pravastatin reduces CV event rates in people who have or are at risk for coronary disease and concomitant moderate CKD, many of whom have serum creatinine levels within the normal range (43). Indeed, there is controversial evidence about the effects of lipid-lowering therapy on rate of kidney loss in people with coronary heart disease. The Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study showed that in untreated dyslipidemic patients with coronary heart disease and normal renal function at baseline, creatinine clearance declines over a period of 3 yr, but statin treatment prevents this decline and significantly improves renal function (44). By contrast, a recent study that included 18,569 patients who had or were at risk for coronary disease, 3402 of whom had moderate CKD, showed that pravastatin modestly reduced the rate of kidney function loss (45). Similarly, there is recent evidence about the efficacy and the safety of low-dose aspirin in patients with CKD (46), although this therapy is underused when CKD is associated with acute myocardial infarction (47,48).

In CKD, there is good evidence about the benefits related to BP control, correction of anemia, treatment of dyslipidemia, cessation of tobacco use, and antiplatelet therapy (49). The relevance of CKD in high-risk patients requires an integrative therapeutic approach to protect fully and simultaneously renal and CV systems (50,51).

Conclusion

CKD is a situation of high added CV risk in hypertensive patients. Strict BP control must be obtained in most cases by combination therapy that must include an ACE or an angiotensin receptor blocker. This must be accompanied by statin and aspirin (the later once BP control has been attained).

References

1. Chobanian A, Bakris GL, Black HR, Cushman W, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella E: 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
2. Guidelines Committee: 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 21: 1011–1053, 2003
3. Ruilope LM, van Veldhuisen DJ, Ritz E, Luscher T: Renal function: The Cinderella of cardiovascular risk profile. *J Am Coll Cardiol* 38: 1782–1787, 2001
4. Sarnak MJ, Levey AS, Schollwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention: 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
5. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 56: 2214–2219, 1999
6. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: 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
7. Clase CM, Garg AX, Kiberd BA: Prevalence of low glomerular filtration rate in nondiabetic Americans: Third National Health and Nutrition Examination survey (NHANES III). *J Am Soc Nephrol* 13: 1338–1349, 2002
8. Segura J, Campo C, Ruilope LM: How relevant and frequent is the presence of mild renal insufficiency in essential hypertension? *J Clin Hypertens (Greenwich)* 4: 332–336, 2002
9. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ: Chronic kidney disease as a risk factor for cardiovascular disease and all cause mortality: A pooled analysis of community-based studies. *J Am Soc Nephrol* 15: 1307–1315, 2004
10. Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, Wakugawa Y, Hata J, Oishi Y, Shikata K, Yonemoto K, Hirakata H, Iida M: Chronic kidney disease and cardiovascular disease in a general Japanese population: The Hisayama Study. *Kidney Int* 68: 228–236, 2005
11. Weiner DE, Tighiouart H, Stark PC, Amin MG, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ: Kidney disease as a risk factor for recurrent cardiovascular disease and mortality. *Am J Kidney Dis* 44: 198–206, 2004
12. Segura J, Campo C, Gil P, Roldan C, Vigil L, Rodicio JL, Ruilope LM: Development of chronic kidney disease and cardiovascular prognosis in essential hypertensive patients. *J Am Soc Nephrol* 15: 1616–1622, 2004
13. Jager A, Kostense PJ, Ruhe HG, Heine RJ, Nijpels G, Dekker JM, Bouter LM, Stehouwer CD: 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
14. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE: Microalbuminuria as predictor of increased mortality in elderly people. *BMJ* 300: 297–300, 1990
15. Dinneen SF, Gerstein HC: The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus: A systematic overview of the literature. *Arch Intern Med* 157: 1413–1418, 1997
16. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S; HOPE Study Investigators: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and non-diabetic individuals. *JAMA* 286: 421–426, 2001
17. Jensen JS, Feldt-Rasmussen B, Strangaard S, Schroll M, Borch-Johnsen K: Arterial hypertension, microalbuminuria and risk of ischemic heart disease. *Hypertension* 35: 898–903, 2000
18. Bigazzi R, Bianchi S, Baldari D, Campese VM: Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. *J Hypertens* 16: 1325–1333, 1998
19. Agewall S, Wikstrand J, Ljungman S, Fagerberg B: Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. *Am J Cardiol* 80: 164–169, 1997
20. Roest M, Banga JD, Janssen WM, Grobbee DE, Sixma JJ, de Jong PD, de Zeeuw D, van Der Schouw YT: Excessive urinary albumin levels are associated with future cardiovascular mortality in postmenopausal women. *Circulation* 103: 3057–3061, 2001
21. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE; Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group: Urinary albumin excretion predicts cardiovascular and non-cardiovascular mortality in general population. *Circulation* 106: 1777–1782, 2002
22. Redon J, Williams B: Microalbuminuria in essential hypertension: Redefining the threshold. *J Hypertens* 20: 353–355, 2002
23. Segura J, Campo C, Ruilope LM: Effect of proteinuria and glomerular filtration rate on cardiovascular risk in essential hypertension. *Kidney Int* 66: S45–S49, 2004
24. Fesler P, Du Cailar G, Ribstein J, Mimran A: Left ventricular remodeling and renal function in never-treated essential hypertension. *J Am Soc Nephrol* 14: 881–887, 2003
25. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH: Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 114: 345–352, 1991
26. Volpe M, Alderman MH, Furberg CD, Jackson R, Kostis JB, Laragh JH, Psaty BM, Ruilope LM: Beyond hypertension toward guidelines for cardiovascular risk reduction. *Am J Hypertens* 17: 1068–1074, 2004
27. Turnbull F: Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: Results of prospectively-designed overviews of randomised trials. *Lancet* 362: 1527–1535, 2003
28. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A; VALUE Trial Group: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet* 363: 2022–2031, 2004
29. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW; INVEST Investigators: A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): A randomized controlled trial. *JAMA* 290: 2805–2816, 2003
30. Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, Zidek W, Dominiak P, Diener HC; MOSES Study Group: Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: Principal results of a prospective randomized controlled study (MOSES). *Stroke* 36: 1218–1226, 2005
31. Poole-Wilson PA, Lubsen J,Kirwan BA, van Dalen FJ, Wagener G, Danchin N, Just H, Fox KA, Pocock SJ, Clayton TC, Motro M, Parker JD, Bourassa MG, Dart AM, Hildebrandt P, Hjalmarson A, Kragten JA, Molhoek GP, Otterstad JE, Seabra-Gomes R, Soler-Soler J, Weber S; A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system investigators: Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): Randomised controlled trial. *Lancet* 364: 849–857, 2004
32. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ; CAMELOT Investigators: Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: The CAMELOT study: A randomized controlled trial. *JAMA* 292: 2217–2225, 2004
33. Wang JG, Staessen JA, Franklin SS, Fagard R, Gueyffier F: Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. *Hypertension* 45: 907–913, 2005
34. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 360: 7–22, 2002
35. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT investigators: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. *Lancet* 361: 1149–1158, 2003
36. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of

the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 351: 1755–1762, 1998
37. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
38. Takemoto M, Liao JK: Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors. *Arterioscler Thromb Vasc Biol* 21: 1712–1719, 2001
39. Borghi C, Dormi A, Veronesi M, Sangiorgi Z, Gaddi A; Brisighella Heart Study Working Party: Association between different lipid-lowering treatment strategies, blood pressure control in the Brisighella Heart Study. *Am Heart J* 148: 285–292, 2004
40. Anavekar NS, Pfeffer MA: Cardiovascular risk in chronic kidney disease. *Kidney Int Suppl* 92: S11–S15, 2004
41. Ezekowitz J, McAlister FA, Humphries KH, Norris CM, Tonelli M, Ghali WA, Knudtson ML; APPROACH Investigators: The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. *J Am Coll Cardiol* 44: 1587–1592, 2004
42. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 351: 1285–1295, 2004
43. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furberg C, Cobbe SM, Simes J, Craven T, West M: Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* 110: 1557–1563, 2004
44. Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, Elisaf M: The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J Clin Pathol* 57: 728–734, 2004
45. Tonelli M, Isles C, Craven T, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furberg C, Cobbe SM, Simes J, West M, Packard C, Curhan GC: Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. *Circulation* 112: 171–178, 2005
46. Baigent C, Landray M, Leaper C, Altmann P, Armitage J, Baxter A, Cairns HS, Collins R, Foley RN, Frighi V, Kourellias K, Ratcliffe PJ, Rogerson M, Scoble JE, Tomson CR, Warwick G, Wheeler DC: First United Kingdom Heart and Renal Protection (UK-HARP-I) study: Biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *Am J Kidney Dis* 45: 473–484, 2005
47. McCullough PA, Sandberg KR, Borzak S, Hudson MP, Garg M, Manley HJ: Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. *Am Heart J* 144: 226–232, 2002
48. Berger AK, Duval S, Krumholz HM: Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. *J Am Coll Cardiol* 42: 201–208, 2003
49. Curtis BM, Levin A, Parfrey PS: Multiple risk factor intervention in chronic kidney disease: Management of cardiac disease in chronic kidney disease patients. *Med Clin North Am* 89: 511–523, 2005
50. Segura J, Campo C, Ruilope LM: Chronic kidney disease and global cardiovascular risk in essential hypertension. *Minerva Med* 95: 375–383, 2004
51. Fioretto P, Solini A: Antihypertensive treatment and multifactorial approach for renal protection in diabetes. *J Am Soc Nephrol* 16[Suppl 1]: S18–S21, 2005