LE JACQ®

Original Paper

Should Hypertension Guidelines Be Changed for Hypertensive Patients With the Metabolic Syndrome?

Julian Segura, MD;[1] Jose Ramon Banegas, MD;[2] Jose Antonio García-Donaire, MD;[1] Fernando Rodríguez-Artalejo, MD;[2] Juan Jose de la Cruz, MD;[2] Manuel Praga, MD;[1] Luis Miguel Ruilope, MD[1]

*The authors analyzed the impact of present guidelines for hypertension management on cardiovascular (CV) risk factors in hypertensive patients with and without the metabolic syndrome (MS). Results in 549 nondiabetic hypertensive patients with a mean follow-up of 3.8±1.2 years on usual recommended care were reviewed. At baseline, 231 (42.1%) patients had MS and, per the definition, showed significantly higher values of traditional CV risk factors than non-MS patients. At the end of follow-up, blood pressure levels were similar in both groups; the lipid profile tended to improve in MS patients. Eighteen MS patients (7.8%) and 7 non-MS patients (2.2%) developed diabetes (*P*<.001). Prevalence of microalbuminuria was reduced in both groups, but it remained significantly higher in MS patients. Usual care of hypertensive patients achieved similar blood pressure and low-density lipoprotein cholesterol goals, both in MS and non-MS patients. Global CV risk, however, remained higher in MS patients, as suggested by a 3-fold higher incidence of new-onset diabetes (absolute increase of 5.6%) and a 2-fold increase in microalbuminuria. (J Clin Hypertens. 2007;9:595–600)* ©2007 Le Jacq

From the Hypertension Unit, Nephrology Department, Hospital 12 de Octubre, Madrid, Spain;[1] and the Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autonoma, Madrid, Spain[2]
Address for correspondence:
Julian Segura, MD, Hypertension Unit, Hospital 12 de Octubre, Av. Córdoba s/n, 28041 Madrid, Spain
E-mail: hta@juliansegura.com
Manuscript received January 7, 2007;
revised May 31, 2007;
accepted May 31, 2007

www.lejacq.com **ID: 6522**

The metabolic syndrome (MS) is associated with an increased risk of type 2 diabetes and cardiovascular morbidity and mortality.[1,2] Insulin resistance is a key component of a constellation of metabolic abnormalities. The most prevalent form of insulin resistance is associated with abdominal obesity and with "dysfunctional" adipose tissue that cannot properly handle the energy surplus that results from a sedentary lifestyle and excessive calorie consumption.[3] MS is prevalent in essential hypertensive patients.[4] The relationship between MS and increased cardiovascular risk has been recognized by most recently published guidelines for the management of hypertension,[5,6] but there are no specific recommendations about the management of these patients at present. The goal for blood pressure (BP) control and other cardiovascular risk factors is similar for nondiabetic hypertensives with and without MS. Lifestyle changes are strongly recommended for treatment,[5–7] and if these lifestyle interventions are not sufficient, then drug therapies for abnormalities in individual risk factors are indicated.[7,8] This approach does not appear to acknowledge the possibility that MS may confer a greater cardiovascular and diabetogenic relative risk beyond that associated with its individual components.[1] The fact that MS increases the risk of a cardiovascular event by a factor of 2 and that of diabetes by a factor of 5[7] suggests that its

Table I. Baseline Characteristics of Patients With and Without the Metabolic Syndrome (MS)			
	Patients With MS	Patients Without MS	P Value
No.	231	318	
Weight, kg	83.1±12.1	73.2±121	<.001
BMI, kg/m^2	30.8±4.0	28.3±4.7	<.001
SBP, mm Hg	153±22	148±22	.020
DBP, mm Hg	92±11	89±11	.002
Antihypertensive drugs, No.	2.1±1	1.8±1	.003
BP control, %	20.6	27.4	.068
Glycemia, mg/dL	107.0±11.4	98.0±8.6	<.001
Total cholesterol, mg/dL	220.0±35.0	216.2±36.9	.228
LDL cholesterol, mg/dL	146.6±31.2	140.8±32.0	.035
HDL cholesterol, mg/dL	44.8±11.5	56.6±12.6	<.001
Triglycerides, mg/dL	146.0±64.9	97.3±35.8	<.001
Serum creatinine, mg/dL	1.05±0.27	0.92±0.24	<.001
Estimated GFR, mL/min/1.73 m^2	94.4±31.3	89.8±30.7	.091
Microalbuminuria, mg/24 h	40.7±92.4	22.8±40.7	.009
Microalbuminuria, %	42.8	29.6	.010
Smokers, %	16.2	15.8	.692

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

presence in a hypertensive patient might indicate a reconsideration of therapeutic approaches and goals in these patients.

Our aim was to retrospectively analyze the impact of usual care for hypertensive patients with MS following European Society of Hypertension/European Society of Cardiology (ESH/ESC) guideline recommendations on control of cardiovascular risk factors, changes in urinary albumin excretion, and development of new-onset diabetes in a series of essential hypertensive patients with and without MS in a hospital-based hypertension unit.

MATERIALS AND METHODS

Study Design

This was an observational, long-term follow-up study of a cohort of nondiabetic essential hypertensive patients attending our hypertension unit to analyze the impact of recommended therapeutic strategies for management of hypertension in patients with known cardiovascular risk factors, with or without the presence of MS.

Patients

We selected nondiabetic patients aged between 18 and 80 years, diagnosed with essential hypertension, and with at least 2 years of follow-up. We excluded patients with malignant hypertension or suspected or diagnosed secondary hypertension and those presenting with evidence of previous cardiovascular disease.

Evaluation and Follow-Up

Complete medical history and physical examination were performed at entry. BP was measured 3 times using a mercury sphygmomanometer after 5 minutes in a seated position, using an adequately sized cuff. BP was measured by trained nurses. The mean of 3 values was considered for the analysis. According to our usual protocol, patients were followed at 3-month intervals for BP measurement and medication adjustment to achieve recommended BP goals (<140/90 mm Hg). Blood samples and 24-hour urine collection were obtained at least twice a year to measure levels of serum creatinine, glucose, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides as well as for the estimation of glomerular filtration rate and 24-hour urinary albumin excretion.

Outcome Variables

MS was defined according to Third Report of the Adult Treatment Panel (ATP III) criteria.[9] This definition requires that at least 3 of the following criteria be present: waist circumference >102 cm in men and >88 cm in women; hypertriglyceridemia ≥150 mg/dL; HDL cholesterol level <40 mg/dL in men and <50 mg/dL in women; BP ≥130/85 mm Hg; and fasting glucose level ≥110 mg/dL. Because waist circumference was unavailable for some patients, we defined abdominal obesity according to body mass index (BMI) ≥27.5 in men and ≥28.5 in women.[10] BP was defined as systolic/diastolic BP

Table II. Characteristics of Patients With and Without the Metabolic Syndrome (MS) at the End of Follow-Up

	Patients With MS	Patients Without MS	*P* Value
No.	231	318	
Weight, kg	83.5±12.1	74.5±13.1	<.001
BMI, kg/m²	30.9±3.9	28.7±4.8	<.001
SBP, mm Hg	139±24	136±19	.128
DBP, mm Hg	81±11	81±9	.449
Antihypertensive drugs, No.	2.4±1.2	2.1±1.2	.003
BP control, %	52.0	58.8	.120
Glycemia, mg/dL	105.2±16.9	97.9±19.9	<.001
Total cholesterol, mg/dL	209.3±33.8	213.1±35.0	.201
LDL cholesterol, mg/dL	133.5±32.0	134.5±30.8	.712
HDL cholesterol, mg/dL	49.1±17.2	57.9±12.7	<.001
Triglycerides, mg/dL	141.1±66.8	104.9±49.4	<.001
Serum creatinine, mg/dL	1.04±0.40	0.90±0.27	<.001
Estimated GFR, mL/min/1.73 m²	98.1±34.4	92.5±32.1	.062
Microalbuminuria, mg/24 h	23.6±51.9	11.1±53.8	.005
Microalbuminuria, %	22.2	10.9	.008
Smokers, %	14.2	13.7	.512

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

<140/90 mm Hg. Elevated urinary albumin excretion was defined as values ≥20 mg/24 h on at least 2 measurements during the last year of follow-up. New-onset diabetes was defined as a confirmed fasting plasma glucose (FPG) level ≥126 mg/dL in at least 2 blood sample tests during the last year of follow-up or the use of antidiabetic therapy.

Therapeutic Approach

During the follow-up period, BP goals were initially based on 1999 World Health Organization/International Society of Hypertension guidelines[11] and since 2003 on the ESH/ESC guidelines[6] for the management of hypertension. A recommended goal BP was set at <140/90 mm Hg during follow-up, according to specific guideline recommendations for nondiabetic patients.[6,11] Standard written instructions about lifestyle changes (weight reduction, smoking cessation, reduction in salt intake, and increase in physical activity) were uniformly recommended in all patients. Pharmacologic intervention was instituted according to BP levels and guidelines recommendations, independent of the presence or absence of MS.[11] Lipid-lowering therapy was administered when needed (LDL cholesterol >130 mg/dL) to achieve LDL cholesterol <130 mg/dL.

Statistical Analyses

For our analysis, we collected data from patients on 2 different visits: when patients were first referred to our unit (baseline visit), and after follow-up (at least 2 years later).

The relationship between qualitative variables at baseline and at the end of follow-up and the absolute differences between both was checked with Pearson chi-square test and Yates correction or Fisher exact probability test if necessary.

To study the relationship between quantitative variables at baseline and at the end of follow-up and the absolute differences between both, we checked the normality of the sample by using Kolmogorov-Smirnov test of normality. In case of a near Gaussian distribution, the Student *t* test was used; otherwise the Mann-Whitney test was used. In addition, analysis of variance was used to adjust the absolute differences for age and sex. A *P* value <.05 was considered statistically significant.

RESULTS

Baseline Characteristics

We included 549 patients (mean age, 54.5±13.5 years; 44.3% male) with a mean follow-up of 3.8±1.2 years. At baseline, 231 patients (42.1%) had MS and showed significantly higher values of weight, BMI, systolic and diastolic BP, FPG level, serum levels of LDL cholesterol and triglycerides, and lower levels of HDL cholesterol than non-MS patients. Positive microalbuminuria (>20 mg/d) was more common in MS than in non-MS patients (42.8% vs 29.6%; *P*=.010). Strict BP control (<140/90 mm Hg) was poorer in MS patients than in patients without MS (20.6% vs 27.4%; *P*=.068) despite a greater number of antihypertensive drugs (2.1 vs 1.8; *P*=.003) (Table I).

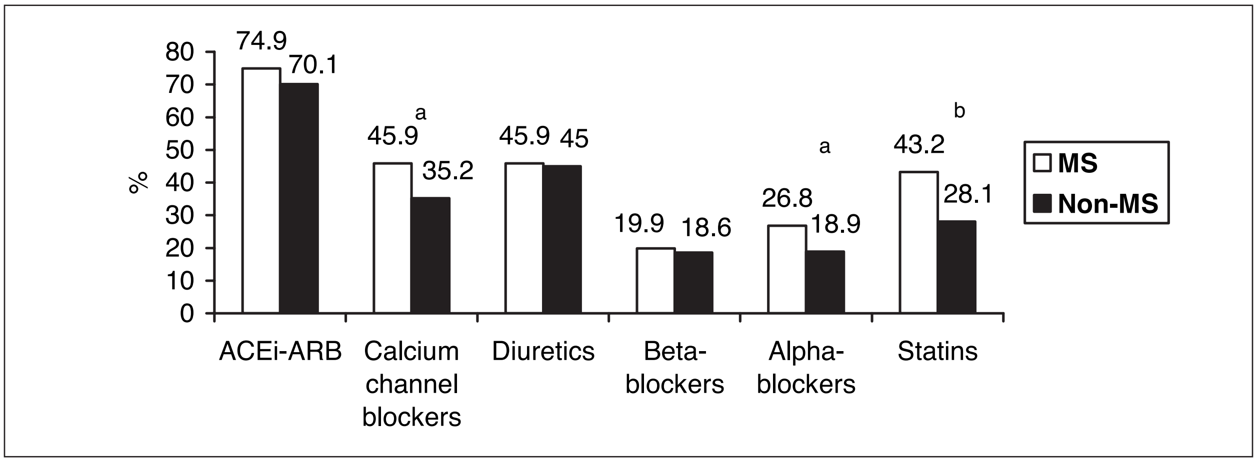

Figure. Percentages of patients receiving antihypertensive and lipid-lowering drugs at the end of follow-up. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MS, the metabolic syndrome. [a]*P<.05.* [b]*P<.001.*

Follow-Up

After a mean follow-up of 3.8±1.2 years, body weight and BMI remained significantly higher in patients with MS compared with those without it. Patients with measured waist circumference showed no significant changes at the end of the follow-up (data not shown). Of interest, systolic and diastolic BP values and percentage of BP control showed no statistically significant differences between groups (52% in MS patients and 58.8% in non-MS patients [Table II]). Levels of total and LDL cholesterol were also similar. HDL cholesterol levels remained lower and serum triglycerides higher among patients with MS but were changed to a significantly greater degree in MS patients. The Figure shows total percentages of patients receiving antihypertensive and lipid-lowering drugs at the final visit. Similar amounts of antihypertensive medications were added during follow-up both in patients with MS and those without it (Table III). Use of calcium channel blockers, a-blockers, and other agents was significantly higher among patients with MS, in comparison with those patients without MS. The percentage of patients presenting with positive microalbuminuria remained significantly higher among those with MS (22.2% vs 10.9%; *P*=.008) (Table II).

Table III shows absolute changes from baseline values in clinical and biochemical characteristics of patients with and without MS at the end of follow-up. After age and sex adjustment, usual care facilitated positive changes in body weight, diastolic BP, and lipid profile in the group of hypertensive patients with MS. In fact, total and LDL cholesterol values and serum triglyceride levels were significantly reduced and HDL cholesterol was increased in patients with MS in comparison with non-MS patients. These changes were related with an increase in lipid-lowering agents administration (Figure). The remaining parameters changed symmetrically in both groups. At the end of follow-up, 18 of 231 patients with MS and 7 of 318 non-MS patients developed new-onset diabetes (7.8% vs 2.2%; *P*<.001).

DISCUSSION

Our results show that usual care of hypertensive patients with MS according to present guidelines may not reduce cardiovascular risk to as great an extent when compared with that of patients without MS, as indicated by more new-onset diabetes and microalbuminuria during follow-up. This was so in the presence of similar degrees of BP and lipid profile control but with the use of more antihypertensive drugs as well as higher doses of statins. Prevalence of microalbuminuria was approximately 10% higher (relative risk, 22.2% vs 10.9%; *P*=.008) and the incidence of new-onset diabetes was approximately 50% higher (18 of 231 patients with MS [7.8%] compared with 7 of 318 patients without MS [2.2%]; *P*<.001). Eighty percent of patients were receiving adequate doses of either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.

Our data confirm previous evidence about the limited benefit of lifestyle changes, in particular body weight changes; a more active intervention in environmental and genetic factors involved in food intake regulation is probably required.[12]

Both patients with and without MS achieved similar BP control; those with MS required more antihypertensive drugs. Control of insulin resistance and BP is the main means to impede the development of endothelial dysfunction and progressive

Table III. Differences in Clinical and Biochemical Characteristics Among Patients With and Without the Metabolic Syndrome (MS) (Final–Baseline)			
	Patients With MS	Patients Without MS	P Value
No.	231	318	
Weight, kg	0.41±6.18	1.37±5.47	.056
BMI, kg/m^2	0.16±2.28	0.47±2.07	.100
SBP, mm Hg	–14.64±28.86	–12.56±24.86	.374
DBP, mm Hg	–10.92±12.18	–8.49±11.47	.019
Antihypertensive drugs, No.	0.34±0.82	0.37±0.771	.936
BP control, %	31.4	31.4	.999
Glycemia, mg/dL	–1.88±16.68	–0.13±19.67	.272
Total cholesterol, mg/dL	–10.66±36.00	–3.07±36.7	.016
LDL cholesterol, mg/dL	–12.53±34.93	–6.40±32.03	.035
HDL cholesterol, mg/dL	4.27±13.50	1.39±10.39	.005
Triglycerides, mg/dL	–4.90±55.35	7.66±44.72	.003
Serum creatinine, mg/dL	–0.02±0.28	–0.01±0.19	.945
Estimated GFR, mL/min/1.73 m^2	1.37±23.68	0.86±20.71	.811
Microalbuminuria, mg/24 h	–9.91±47.74	–9.66±48.77	.960
Microalbuminuria, %	–20.6	–18.7	.516
Smokers, %	–2.0	–2.1	.890

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

atherosclerosis in MS.[13] Recent guidelines recommend a lower BP goal for diabetic patients, but specific recommendations for patients presenting with MS are lacking despite their increased cardiovascular risk.[2] Lorenzo and colleagues[2] consider that men older than 45 years presenting with MS may be eligible for the same therapeutic recommendations as people with multiple risk factors and a 10-year coronary heart disease risk of 10% to 20%.

Increased LDL cholesterol levels are not included in the definition of MS,[9] but in our experience this occurs frequently in MS patients.[4] It has been suggested that patients with MS and normal LDL cholesterol have a cardiovascular risk comparable to those without MS and high LDL cholesterol.[14] Our results demonstrate that it is possible to reduce LDL cholesterol values in patients with MS to values similar to those in patients without it. Nevertheless, it should be noted that there have been few randomized clinical trials based on patients with the current definitions of MS to determine the best treatment for LDL cholesterol control.[15]

Microalbuminuria is an independent predictor of cardiovascular morbidity and mortality in patients with essential hypertension.[16,17] Increased urinary albumin excretion values have been demonstrated in patients with MS,[4] which reflected generalized endothelial dysfunction, an elevated risk for atherosclerosis, and progressive renal disease.[18] The presence of microalbuminuria confers the strongest risk of cardiovascular death to patients with MS.[19] At baseline, we found urinary albumin excretion significantly higher in patients with MS. Similar numerical reductions of urinary albumin excretion were observed in patients with and without MS (–20.6% vs –18.7%; P=.516 [Table III]), but prevalence of microalbuminuria remained significantly higher among patients with MS at the end of follow-up, despite similar percentages of patients receiving a drug indicated to suppress the renin–angiotensin system (RAS) in adequate doses. It is possible that the achievement of better BP control might diminish the amount of urinary albumin excretion.

Blood glucose levels constitute an independent cardiovascular risk factor.[20] The risk starts below the current threshold for the diagnosis of diabetes mellitus.[21] Baseline differences in FPG levels remained unchanged between groups at the end of follow-up because we did not introduce specific pharmacologic therapy to reduce the serum glucose level or to prevent the development of diabetes. It should be noted, however, that there were significant differences in the percentage of new-onset diabetes between patients with MS and those patients without MS in the presence of similar use of diuretics and β-blockers, which are usually considered to be possibly related to new-onset diabetes. There was a higher percentage of patients with MS receiving calcium channel blockers and α-blockers with neutral or positive effects on glucose metabolism and insulin sensitivity.[20,22] The type of antihypertensive therapy has been shown to correlate with the development of new-onset diabetes,[22] although data on its clinical significance are controversial. As expected, more new-onset diabetes appeared in patients with MS, occurring while suppression of RAS was present in most patients.

Our study had limitations related to its retrospective character and to the absence of a randomized distribution of antihypertensive therapies. Moreover, interim data about glycemic control and albumin excretion were not available for many patients during follow-up. Nevertheless, to avoid new-onset diabetes or microalbuminuria overdiagnosis, we only classified as diabetic or microalbuminuric those patients with at least 2 positive measurements of serum glucose or urinary albumin excretion in the last year of follow-up.

CONCLUSIONS

Our data indicated that the implementation of guidelines for management of essential hypertension and cardiovascular risk factors results in the achievement of similar BP and LDL cholesterol goals, both in MS and non-MS patients. Hypertensive patients with MS present with a higher incidence of new-onset diabetes and of urinary albumin excretion. This was accompanied by persistently lower levels of HDL cholesterol and elevated triglyceride levels and BMI. The importance of lowering the therapeutic goals for BP and other cardiovascular risk factors as well as the possibility of new therapeutic approaches should be tested in hypertensive patients with MS.

References

1. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death. *J Am Coll Cardiol*. 2007;49:403–414.
2. Lorenzo C, Hunt KJ, Williams K, et al. The National Cholesterol Education Program-Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care*. 2007;30:8–13.
3. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444:881–887.
4. Segura J, Campo C, Roldan C, et al. Hypertensive renal damage in metabolic syndrome is associated with glucose metabolism disturbances. *J Am Soc Nephrol*. 2004;15(suppl 1):S37–S42.
5. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
6. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens*. 2003;21:1011–1053.
7. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735–2752.
8. Kahn R, Buse J, Ferrannini E, et al. The metabolic syndrome: time for a critical appraisal. Joint statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2005;28:2289–2304.
9. 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*. 2001;285:2486–2497.
10. Design, rational, and baseline characteristics of the Prospective Pravastatin Pooling (PPP) project–a combined analysis of three large-scale randomized trials: Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), Cholesterol and Recurrent Events (CARE), and West of Scotland Coronary Prevention Study (WOSCOPS). *Am J Cardiol*. 1995;76:899–905.
11. Guidelines Subcommittee of the World Health Organization-International Society of Hypertension (WHO-ISH) Mild Hypertension Liaison Committee. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens*. 1999;17:151–183.
12. Haslam DW, James WPT. Obesity. *Lancet*. 2005;366:1197–1209.
13. Lteif AA, Han K, Mather KJ. Obesity, insulin resistance, and the metabolic syndrome: determinants of endothelial dysfunction in whites and blacks. *Circulation*. 2005;112:32–38.
14. Jeppesen J, Hansen TW, Rasmussen S, et al. Metabolic syndrome, low-density lipoprotein cholesterol, and risk of cardiovascular disease: a population-based study. *Atherosclerosis*. 2006;189:369–374.
15. Bestermann W, Houston MC, Basile J, et al. Addressing the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome in the Southeastern United States, part II: treatment recommendations for management of the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome. *Am J Med Sci*. 2005;329:292–305.
16. Ruilope LM, van Veldhuisen DJ, Ritz E, et al. Renal function: the Cinderella of cardiovascular risk profile. *J Am Coll Cardiol*. 2001;38:1782–1787.
17. 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*. 2003;139:901–906.
18. El-Atat FA, Stas SN, McFarlane SI, et al. The relationship between hyperinsulinemia, hypertension and progressive renal disease. *J Am Soc Nephrol*. 2004;15:2816–2827.
19. Palaniappan L, Carnethon M, Fortmann SP. Association between microalbuminuria and the metabolic syndrome: NHANES III. *Am J Hypertens*. 2003;16:952–958.
20. Segura J, Campo C, Ruilope LM, et al. Do we need to target “prediabetic” hypertensive patients? *J Hypertens*. 2005;23:2119–2125.
21. The DECODE study group on behalf of the European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care*. 2003;26:688–696.
22. Mancia G, Grassi G, Zanchetti A. New-onset diabetes and antihypertensive drugs. *J Hypertens*. 2006;24:3–10.