THE RISK OF AN INCIDENCE OF THE CEREBRAL VASCULAR STROKE CORRELATED WITH THE HTA AND HVS IN THE ELDERLY HYPERTENSIVE TREATED WITH ACEI AND BRA

MARIANA ADĂMUŢIU[1], IOAN MANIŢIU[2]

[1]County Emergency Hospital Alba Iulia, [2]"Lucian Blaga" University of Sibiu

Keywords: *hypertension, cerebral vascular stroke, ACEI, BRA, elderly*

Abstract: *For each life decade that elapses after the age of 55, the rate of appearance of the cerebral vascular strokes doubles, more than 80% of the cases of cerebral vascular strokes appear after the age of 65. The high arterial pressure is the main risk factor for all types of cerebral vascular strokes. Left ventricular hypertrophy represents an increased risk factor in the case of morbidity and mortality through cerebral vascular illnesses. Numerous studies (PROGRESS, SCOPE, LIFE, HYVET, SYST-EURO) show that drug blocking of the rennin angiotensin system is important in order to prevent cerebral vascular strokes.(1-3) The treatment of the arterial hypertension prevents the development of a cerebral vascular stroke.*

Cuvinte cheie: *hipertensiune, accident vascular cerebral, ACEI, BRA, vârstnic*

Rezumat: *Pentru fiecare decadă de viaţă după 55 de ani, rata de apariţie a accidentelor vasculare cerebrale se dublează, mai mult de 80% din cazurile de accidente vasculare cerebrale apar după vârsta de 65 de ani. Hipertensiunea arterială este factorul de risc principal pentru toate tipurile de accidente vasculare cerebrale. Hipertrofia ventriculară stângă reprezintă un factor de risc crescut pentru morbiditatea şi mortalitatea prin afecţiuni cerebrovasculare. Numeroase studii (PROGRESS, SCOPE, LIFE, HYVET, SYST-EURO) arată că blocarea medicamentoasă a sistemului renină angiotensină este importantă pentru prevenirea accidentelor vasculare cerebrale. Tratamentul hipertensiunii arteriale previne dezvoltarea unui accident vascular cerebral.*

The brain is a target organ precociously affected by high blood pressure (4), the major liable to influence risk factor for the ischemic and hemorrhagic cerebral vascular stroke.(5) The cerebral vascular stroke represents the second cause of mortality world wide.

The cerebral vascular risk grows gradually with the values of the arterial tension. The relative risk of cerebral stroke is multiplied by 4 in hypertensive persons for arterial tension values superior to 160/90 mm Hg. The SHEP study (Systolic Hypertension in the Elderly Program) has demonstrated that the treatment of the systolic arterial hypertension at subjects aged 60 and more, reduces with 36% the incidence of the cerebral vascular strokes.(6)

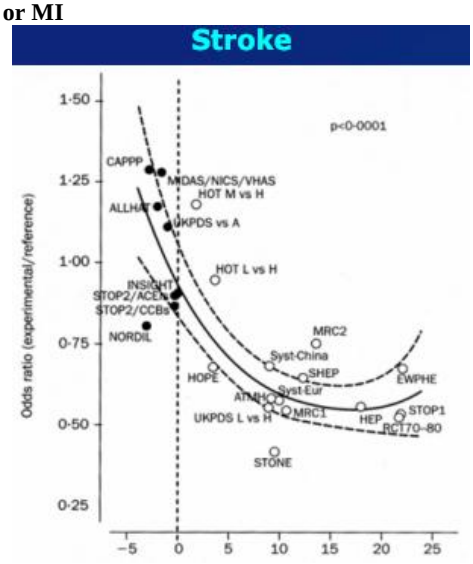
The ischemic, hemorrhagic and degenerative cerebral affections represent a major health problem, particularly in elderly, determining the loss of their autonomy.

After the age, the arterial hypertension represents the most important risk factor in the case of the lesions of the cerebral white substance, which represents an important prognostic factor for the cerebral vascular stokes, the cognitive ailments, madness and death.

The hypertensive patients show a faster rate of the development of the lesion of the white substance compared to those that are normo-tensive.(7,8)

The cerebral vascular stroke is a major cause for the disability and death, and its incidence grows in line with the age and the values of the arterial tension.(9,10)

Figure no. 1. Correlation between Reduction in SBP and Stroke or MI



Difference (reference minus experimental) in systolic pressure (mm Hg)

Staessen et al. Lancet 2001; 358:1305-15

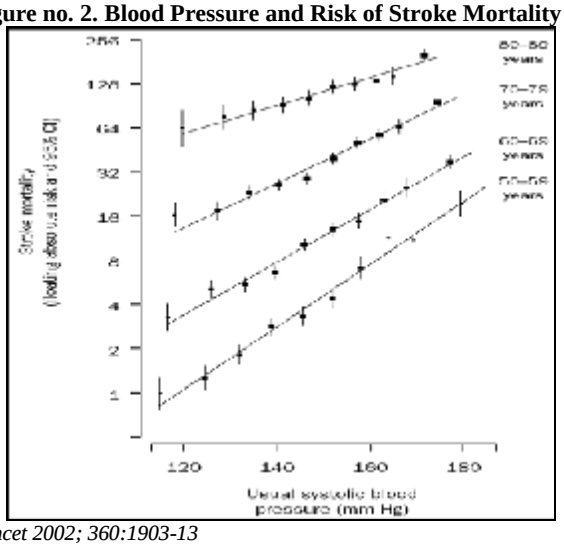
The history of the arterial hypertension represents the most important risk factor for the development of a cerebral vascular stroke, especially a hemorrhagic one.(11)

[1]Corresponding author: Mariana Adămuţiu, Bd. Revoluţiei 1989, Nr. 23, Cod 510160, Alba Iulia, România, E-mail: mariana_adamutiu@yahoo.com, Tel: +0258 821694

Article received on 08.04.2013 and accepted for publication on 30.07.2013

ACTA MEDICA TRANSILVANICA September 2013;2(3):354-358

Figure no. 2. Blood Pressure and Risk of Stroke Mortality



Lancet 2002; 360:1903-13

The risk factors involved in the development of a cerebral vascular stroke can be grouped as follows:

1. Not liable to influence
   - age
   - sex
   - low birth weight
   - genetic predisposition

2. Liable to influence
   - arterial hypertension
   - chronic atrial fibrillation
   - diabetes mellitus
   - dyslipidemia
   - exposure to cigarette smoke
   - sickle cell anemia
   - sedentary activities
   - obesity

3. Liable to potential influence
   - excessive alcohol consumption
   - drugs abuse
   - contraceptive administration per bone
   - sleep disorders

Arterial hypertension remains the most important liable to influence risk factor in the development of a cerebral vascular stroke (12,13,14) and its treatment represents the most important strategy in the prevention of its installation.(15)

The increased arterial tension is an independent risk factor of the installation of carotid atherosclerosis being also helped by the age, sex (the masculine one more frequently), smoking and the level of the serum cholesterol.(16,17) The big tensional values determine, in time, the growth of the thickness of the average pressure, hyaline degeneration, fibrinoid necrosis, narrowing of the lumen, formation of micro-aneurisms at the level of the small perforating arteries and of the cerebral intra-parenchyma arterioles, simultaneously with an inadequate development of the collateral circulation.(18,19)

The re-analysis of the European Guide for the management of the arterial hypertension in 2009 shows the fact that from a group of 192 untreated hypertensive patients, aged between 18 and 90 years, without any detectable cardiovascular diseases, the cerebrovascular silent lesions (the lesions of the white substance, lacunary infarction, cerebral micro-hemorrhages) were more numerous (44%) than the cardiac (25%) or renal (26%) ones.(20,21)

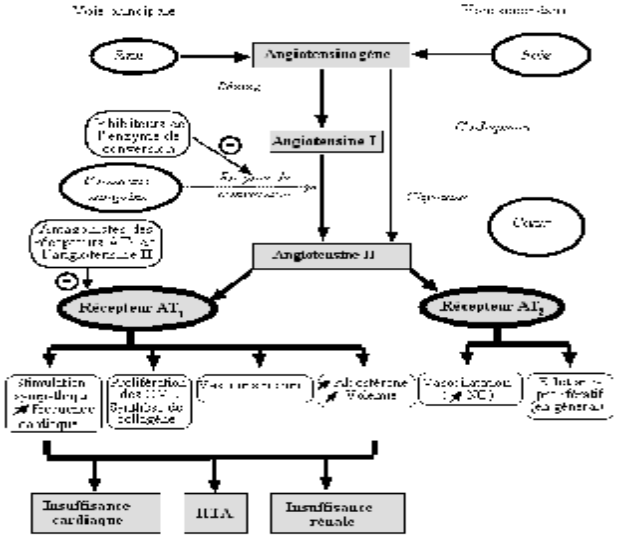
The left ventricular hypertrophy represents an independent risk factor in the case of the morbidity and mortality through cardiovascular diseases at the hypertensive patients. Bikkina and the collaborators (22) show the association between the left ventricular mass and the increased risk of the cerebrovascular events (hemorrhagic vascular accidents, transitory ischemic accidents) present in the old patients enrolled in the Framingham study. It is suggested that the pattern of the geometry of the left ventricle provides information regarding the development of the cardiovascular diseases (23) and the presence of the lesions of the target organ in arterial hypertension.(24,25) The patients suffering of concentric left ventricular hypertrophy develop lesions of target organ at the renal level, more precocious at the retina level than those with a different (eccentric) geometry of the left ventricular hypertrophy. Some studies have found associations between the left ventricular hypertrophy and the cerebral white substance lesions (25-30), some have not.(31) It was proved the existence of a close relationship between the silent lesions of the cerebral white substance and the left ventricular hypertrophy in patients with an untreated arterial hypertension.(29)

The arterial hypertension is considered a major risk factor in the case of the Alzheimer disease and the vascular madness. A reduced control of the arterial tension values is also associated with a decline of the cognitive function.(32,33) The incidence of the cerebral vascular stroke (ischemic or hemorrhagic) increases after a transitory ischemic stroke in the presence of the arterial hypertension or any other cardiovascular risk factors. Lewington underlines the direct link between the incidence of the cerebral vascular stroke and the level of the systolic and diastolic arterial tension for any age group, especially for elderly.(10)

An increased arterial tension in the morning at an elderly hypertensive is associated with an increased risk of developing a cerebral vascular stroke, irrespective of the diurnal or nocturnal tensional values.(34) The reduction of the arterial tension values in the morning represents a new goal from a therapeutic point of view with the aim to prevent the early damage of the target organ in hypertensive disease.

The rennin angiotensin system is involved in the maintenance of a normal hemodynamic status. The self-regulation of the cerebral circulation maintains a constant sanguine flow at the brain level by vasodilatation when the arterial tension lowers and by vasoconstriction when the arterial tension grows. Through angiotensin II it has a vasoconstrictor role, modulating the vascular growth through two types of receptors, having opposite functions (AT1 and AT2). Excessive stimulation of AT1 receptors determines mito-genesis in excess with reduction of vascular compliance, alteration of the NO production, growth of the inflammatory reaction, these all representing characteristic reactions of the blood vessels in arterial hypertension. Blocking the AT1 receptors through antagonists of the angiotensin receptors determines the inversion of the mitosis and of the inflammation pathology, improves the cerebrovascular compliance, ameliorating the NO production. These effects determine the reduction of the brain vulnerability to ischemia and if a cerebral vascular stroke takes place, it protects the sanguine flow in the penumbra area with a substantial reduction of the neuronal injury.(35) The stimulation of the AT2 receptors antagonises the effects of the stimulation of the AT1 receptors.(36-39) In the brain there are AT2 receptors both in the vascular system and the thalamus, hypothalamus, basal nuclei.(40,41)

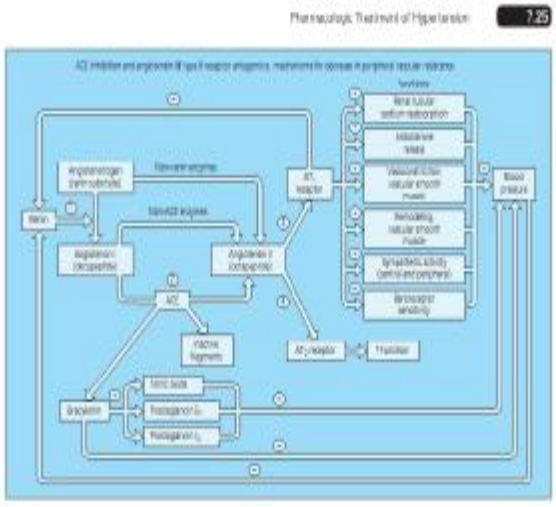
Figure no. 3. Renin-angiotensin-aldosterone system



The use of the inhibitors of the angiotensin conversion enzyme (ACEI) in the treatment of the arterial hypertension determines the reduction of the vascular hypertensive remodelling, the reduction of the left ventricular hypertrophy, all these phenomena being correlated with the growth of the arterial tension. It directly influences the relaxation and the compliance of the myocardium through the diminishing of the deposition of the interstitial collagen and of the fibrosis, processes mediated by the angiotensin.(42,43) A meta- analysis of 109 studies found ACEI as the most efficient in the reduction of the left ventricular hypertrophy.(44)

The treatment with blockers of angiotensin II receptors (BRA), antagonists of AT1 receptors determine the inhibition of the direct vasoconstrictor effect of the angiotensin II thus preserving the vasodilatation effect mediated by the AT2 receptors. The LIFE study (Losartan Intervention for End point reduction in hypertension) underlines the neuro-protecting effect of the blockers of the angiotensin II receptors independently of the one that reduces arterial tension. After the Losartan administration the following are observed: a growth of the density of the small cortical vessels, a reduction of the platelet aggregation and a lowering in the uric acid concentration, while we all know that an increased platelet aggregation correlated with a high level of uric acid are associated with major cardiovascular and cerebral complications.(45-48)

Figure no. 4. Tratamentul farmacologic al hipertensiunii



In the majority of the studies, the reduction of the risk of developing a cerebral vascular stroke is in concordance with the reduction of the arterial tension values. A reduction of the arterial tension with 10 mmHg leads to a reduction of 20% even 30 % of the risk of cerebral vascular stroke. This happens when the comparisons are made between groups of patients treated placebo and with anti-hypertensive medicines.(49)

Table no. 1. Stroke incidence from prospective randomized clinical trials using angiotensin converting enzyme inhibitors and angiotensine receptor blockers

Table 1. *Stroke incidence from prospective, randomized clinical trials using angiotensin converting enzyme inhibitors and angiotensin receptor blockers.*

STUDY (Ref)	SUBJECT PATHOLOGY	NUMBER PATIENTS	FOLLOW-UP Years	TREATMENT	INCIDENCE OF STROKE (%)
PROGRESS[1]	Post-Stroke	6,105	4.0	Perindopril vs Placebo	5.0% Decrease
CAPP[50]	Hypertensive	10,985	6.1	Captopril vs Diuretics, beta-blockers	25% Increase
ALLHAT[4]	Hypertensive	24,909	4.9	Lisinopril vs chlorthalidone	15% Increase
ANBP2[2]	Elderly Hypertensive	6,083	4.1	Enalapril vs HCTZ	Total No Change
HOPE[51]	Mostly normotensive with CAD, PVD	9,297	1.5	Ramipril vs Palcebo	32% Decrease
DIABHYCAR[52]	Diabetic with MA	4,912	4.0	Ramipril vs Placebo	No Change
LIFE[3]	Hypertensive with LVH	9,193	4.5	Losartan vs Atenolol	25% Decrease
LIFE-ISH[6]	Elderly Hypertensive	1,326	4.7	Losartan vs Atenolol	40% Decrease
SCOPE[7]	Elderly Hypertensive	4,937	5.0	Candesartan vs. Conventional Drugs	28% Decrease
SCOPE-ISH[8]	Elderly Hypertensive	1,518	5.0	Candesartan vs Conventional Drugs	42% Decrease
ACCESS-PILOT[53]	Post-Stroke	33.9	1.0	Candesartan vs Placebo	52% Decrease
VALUE[5]	High Risk Hypertensive	15,245	4.2	Valsartan vs Amlodipine	25% Decrease*

LVH = Left ventricular hypertrophy - ISH = Isolated systolic hypertension
*Valsartan decreased stroke by the end of study, but the overall stroke incidence was 15% higher.
Modified with permission from Chrysant SG[54]

Acknowledgement:

Research done as part of the SOPHRD (POSDRU) Project /88/1.5/S/60370 subsidised through European Social Fund in accordance with theHuman Resources Development Operational Programme 2007-2013.

REFERENCES

1. Dahlöf B, Devereux RB, Kjeldsen SE, et al, LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359:995-1003.
2. Lithell H, Hansson L, Skoog I, et al. SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens. 2003;21:875-886.
3. Schiffrin EL. Progress in secondary prevention of stroke with PROGRESS. The Perindopril Protection Against Recurrent Stroke study. Curr Hypertens Rep. 2002;4:39-40.
4. Mancia G, De Backer G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the EuropeanSociety of Cardiology (ESC), Journal of Hypertension. 2007;25(6):1105-1187.
5. Goldstein LB, Bushnell CD, Adamsetal RJ. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke. 2010;42:517-584.
6. SHEP Cooperation Research Group, Prevention of stoke by antihypertensive drug treatment in olders persons with isolated systolic hypertension: final results of the systolic

Hypertension in the Ederly Program (SHEP). JAMA 1991;365:3255-64.
7. Pantoni L, Garcia JH. The significance of cerebral white matter abnormalities 100 years after Binswanger's report: a review, Stroke. 1995;26:1293-1301.
8. Liao D, Cooper L, Cai J, et al. Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control. The ARIC study, Stroke. 1996;27:2262-2270.
9. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection Evaluation, and TReatment of High Blood Pressure (JNC-7) Hypertension. 2003;42:1206-1252.
10. Lewington S, Clark R, Quizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a metaanalysis of individual data from one million adults in 61 prospective studies. Prospective Studies Collabooration. Lancet. 2002;360:1903-1913.
11. Tu JV. Reducing the global burden of stroke: INTERSTROKE" Lancet 2010; DOI: 10.1016/S0140-6736(10)60975-0.
12. American Heart Association. 2000 Heart and Stroke Statistical Update. Dallas, Tex: American Heart Association; 1999.
13. Kannel WB, Wolf PA, Verter J, McNamara PM. Epidemiologic assessment of the role of blood pressure in stroke: the Framingham Study. JAMA. 1970;214:301-310.
14. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke. 1991;22:312-318.
15. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., Jones DW, Materson BJ, Oparil S, Wright JT Jr., Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560-2572.
16. Wilson PW, Hoeg JM, D'Agostino RB, et al. Cumulative effects of high cholesterol levels, high blood pressure and cigarette smoking on carotid stenosis. N Engl J Med. 1997;337:516-522.
17. Fine-Edelstein JS, Wolf PA, O'Leary DH, et al. Precursors of extracranial carotid atherosclerosis in the Framingham Study. Neurology. 1994;44:1046-1050.
18. Hedera P, Bujdakova J, Traubner P, Pancak J. Stroke risk factors and the development of collateral flow in carotid occlusive disease. Acta Neurol Scand. 1998;98:182-186.
19. Johansson BB, Fredriksson K. Cerebral arteries in hypertension: structural and hemodynamic aspects. J Cardiovasc Pharmacol. 1985;7(suppl 2):S90-S93.
20. G. Mancia, S. Laurent, E. Agabiti-Rosei et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force documental, Blood Pressure. 2009;27:2121-2158.
21. Henskens LH, Van Oostenbrugge RJ, Kroon AA, Hofman PA, Lodder J, De Leeuw PW. Detection of silent cerebrovascular disease refines risk stratification of hypertensive patients, Journal of Hypertension. 2009;27(4):846-853.
22. Bikkina M, Levy D, Evans JC, et al. Left ventricular mass and risk of stroke in an elderly cohort: the Framingham heart study, Journal of the American Medical Association. 1994;272(1):33-36.
23. Shigematsu Y, Hamada M, Ohtsuka T, et al. Left ventricular geometry as an independent predictor for extracardiac target organ damage in essential hypertension, American Journal of Hypertension. 1998;11(10):1171-1177.
24. Pontremoli R, Ravera M, Bezante GP, et al. Left ventricular geometry and function in patients with essential hypertension and microalbuminuria, Journal of Hypertension. 1999;17(7):993-1000.
25. Lindgren A, Roijer A, Rudlinget O, al. Cerebrallesionson magnetic resonance imaging, heart disease, and vascular risk factors in subjects without stroke: a population-based study, Stroke. 1994;25(5)929-934.
26. Longstreth WT, Manolio TA, Arnoldetal A. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The cardiovascular health study, Stroke. 1996;27:1274-1282.
27. Schmidt R, Hayn M, Fazekas F, Kapeller P, Esterbauer H. Magnetic resonance imaging white matter hyperintensities in clinically normal elderly individuals. Correlations with plasma concentrations of naturally occurring antioxidants, Stroke. 1996;27(11):2043-2047.
28. Kohara K, Zhao B, Jiang Y, et al. Relation of left ventricular hypertrophy and geometry to asymptomatic cerebrovascular damage in essential hypertension, American Journal of Cardiology. 1999;83(3):367-370.
29. Sierra C, de la Sierra A, Par´ JA, Omez-Angelats EG, Coca A. Correlation between silent cerebral white matter lesions and left ventricular mass and geometry in essential hypertension, American Journal of Hypertension. 2002;15(6):507-512.
30. Fox ER, Taylor HA Jr, Benjamin EJ, et al. Left ventricular mass indexed to height and prevalent MRI cerebrovascular disease in an African American cohort: the atherosclerotic risk in communities study, Stroke. 2005;36(3):546-550.
31. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T.M lent cerebrovascular disease in the elderly. Correlation with ambulatory pressure, Hypertension. 1990;16(6):692-699.
32. Vinyoles E, De la Figuera M, Gonzalez-Segura D. Cognitive function and blood pressure control in hypertensive patients over 60 years of age: COGNIPRES study. Curr Med Res Opin. 2008;24:3331-9.
33. Sacktor N, Gray S, Kawas C, et al. Systolic blood pressure within an intermediate range may reduce memory loss in an elderly hypertensive cohort. J Geriatr Psychiatry Neurol. 1999;12:1-6.
34. Circulation. 2003; 107: 1401-1406 Published online before print March 3, 2003, doi: 10.1161/01.CIR.0000056521.67546.AA
35. Benicky J, Sánchez-Lemus E, Jaroslav P, Saavedra JM. Anti-Inflammatory Effects of Angiotensin Receptor Blockers in the Brain and the Periphery Cellular and Molecular Neurobiology. 2009;29:(6-7):781-792
36. De Gasparo M, Catt KJ, Inagami T, et al. International Union of Pharmacology, XXIII: the angiotensin II receptors. Pharmacol Rev. 2000;52:415-472.
37. Horiuchi M, Akishita M, Dzau VJ. Recent progress in angiotensin II type 2 receptor research in the cardiovascular system. Hypertension. 1999;33:613-621.
38. Kaschina E, Unger T. Angiotensin AT1/AT2 receptors: regulation, signalling and function. Blood Press. 2003;12:70-88.
39. Gallinat S, Busche S, Raizada MK, et al. The angiotensin II type 2 receptor: an enigma with multiple variations. Am J Physiol. 2000;278: E357-E374.
40. Jöhren O, Imboden H, Häuser W, et al. Localization of angiotensin-converting enzyme, angiotensin II, angiotensin II receptor subtypes, and vasopressin in the mouse hypothalamus. Brain Res. 1997;757:218-227.

41. Häuser W, Jöhren O, Saavedra JM. Characterization and distribution of angiotensin II receptor subtypes in the mouse brain. Eur J Pharmacol. 1998;348:101-114.
42. De Simone G, Izzo R, Chinali M, De Marco M, Casalnuovo G, Rozza F, Girfoglio D, Iovino GL, Trimarco B, De Luca N. Does information on systolic and diastolic function improve prediction of a cardiovascular event by left ventricular hypertrophy in arterial hypertension? Hypertension. 2010;56:99-104.
43. Schillaci G, Pasqualini L, Verdecchia P, Vaudo G, Marchesi S, Porcellati C, de Simone G, Mannarino E. Prognostic significance of left ventricular diastolic dysfunction in essential hypertension. J Am Coll Cardiol. 2002; 39:2005-2011
44. Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Ann Intern Med. 1997;127:337-345.
45. Lehto S, Niskanen L, Ronnemaa T, et al. Serum uric is a strong predictor of stroke in patients with non-insulin dependent diabetes mellitus. Stroke. 1998;29:635-639.
46. Verdecchia P, Schillaci G, Reboldi GP, et al. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA Study. Hypertension. 2000;36:1072-1078.
47. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality, the NHanesi epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. JAMA. 2000;283:2404-2410.
48. Johnson RJ, Kang DH, Feig D, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003;41:1183-1190.
49. Lawes CM, Bennett DA, Feigin VL, et al. Blood pressure and stroke: an overview of published reviews. Stroke. 2004;35:776-85.