Effects of Different Classes of Antihypertensive Agents on the Outcome of Acute Ischemic Stroke

Konstantinos Tziomalos, MD, PhD; Vasilios Giampatzis, MD; Stella D. Bouziana, MD; Marianna Spanou, MD; Maria Papadopoulou, MD; Pavlina Kazantzidou, MD; Stavroula Kostaki, MD; Antonios Kouparanis, MD; Christos Savopoulos, MD, PhD; Apostolos I. Hatzitolios, MD, PhD

From the First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece

It is unclear whether antihypertensive treatment before stroke affects acute ischemic stroke severity and outcome. To evaluate this association, the authors studied 482 consecutive patients (age 78.8±6.7 years) admitted with acute ischemic stroke. Stroke severity was assessed at admission with the National Institutes of Health Stroke Scale (NIHSS). The outcome was assessed with rates of adverse outcome (modified Rankin scale at discharge ≥2). Independent predictors of severe stroke (NIHSS ≥16) were female sex and atrial fibrillation. Treatment with diuretics before stroke was associated with nonsevere stroke. At discharge, patients with adverse outcome were less likely to be treated before stroke with β-blockers or with diuretics. Independent predictors of adverse outcome were older age, higher NIHSS at admission, and history of ischemic stroke. Treatment with diuretics before stroke appears to be associated with less severe neurologic deficit in patients with acute ischemic stroke. *J Clin Hypertens (Greenwich).* 2015;17:275–280.

Stroke represents a leading cause of mortality and the first cause of functional disability in the developed world.[1] Hypertension is the most important modifiable risk factor for stroke.[2] Moreover, antihypertensive treatment significantly reduces the risk of first and recurrent stroke.[2–5] In contrast, poor adherence to antihypertensive treatment is associated with increased incidence of cerebrovascular events.[6,7]

Large meta-analyses suggest that the major classes of antihypertensive agents (ie, β-blockers, diuretics, calcium channel blockers [CCBs], angiotensin-converting enzyme [ACE] inhibitors, and angiotensin receptor blockers [ARBs]) yield comparable reductions in the risk for stroke.[4,5] However, direct comparisons between different antihypertensive classes are limited and therefore the optimal antihypertensive agent for reducing the risk of stroke is uncertain.[3] However, in the setting of acute stroke, experimental data suggest that some antihypertensive agents have direct neuroprotective effects that can reduce stroke severity and improve functional outcome.[8] However, controversial clinical data have been reported regarding the effect of the use of different classes of antihypertensive drugs before stroke on acute ischemic stroke severity and outcome.[9–14] Some studies have reported a beneficial effect of pretreatment with β-blockers,[12] CCBs,[14] ACE inhibitors,[10,11] or ARBs.[9] In contrast, others have not identified an association between antihypertensive treatment and stroke severity or outcome[13] or reported an adverse effect of diuretics[10] or β-blockers.[14]

The aim of the present study was to evaluate the effect of treatment with the five main categories of antihypertensive agents before stroke on stroke severity, functional outcome at discharge, and in-hospital mortality in patients hospitalized with acute ischemic stroke.

PATIENTS AND METHODS

We studied all patients who were admitted to our department with acute ischemic stroke between September 2010 and June 2013 (n=482; 40.2% men, age 78.8±6.7 years).

At admission, demographic data (age, sex), history of cardiovascular risk factors (hypertension, type 2 diabetes mellitus, atrial fibrillation, smoking, alcohol consumption, family history of premature cardiovascular disease (CVD), chronic kidney disease), history of concomitant CVD (coronary heart disease, previous stroke, congestive heart failure), and pharmacologic treatment were recorded. Anthropometric parameters (weight, height, waist and hip circumference, waist to hip ratio) and systolic blood pressure and diastolic blood pressure (DBP) were also measured. The severity of stroke was assessed at admission with the National Institutes of Health Stroke Scale (NIHSS). Stroke was classified as severe (NIHSS score at admission ≥16) and nonsevere (NIHSS score at admission ≤15).

Routine laboratory investigations were performed after overnight fasting on the first day after admission and included serum levels of glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, creatinine, and uric acid. Low-density lipoprotein cholesterol levels were calculated using Friedewald's formula.[15] Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease

Address for correspondence: Konstantinos Tziomalos, MD, PhD, First Propedeutic Department of Internal Medicine, AHEPA Hospital, 1 Stilponos Kyriakidi street, Thessaloniki, 54636, Greece
E-mail: ktziomalos@yahoo.com

Manuscript received: October 7, 2014; **revised:** November 23, 2014; **accepted:** November 25, 2014
DOI: 10.1111/jch.12498

equation.[16] Chronic kidney disease was defined as estimated GFR <60 mL/min/1.73 m^2.

All patients underwent brain computed tomography at admission and a second brain computed tomography was performed if clinically indicated.

The outcome was assessed with the modified Rankin scale (mRS) at discharge and with in-hospital mortality. Adverse outcome was defined as mRS at discharge ≥2. This cutoff was used because it separates patients who are independent (ie, have mRS 0 or 1) from those who have some degree of dependency (ie, have mRS between 2 and 5) or are dead (ie, mRS 6).

Statistical Analysis

All data were analyzed with the statistical package SPSS (version 17.0; SPSS, Chicago, IL). Data are presented as percentages for categorical variables and as mean and standard deviation for continuous variables. Differences in categorical variables between groups were assessed with the chi-square test. Differences in continuous variables between groups were assessed with one-way analysis of variance and post hoc tests were performed with the Holm-Sidak test. Binary logistic regression analysis was used to identify independent predictors of severe stroke, adverse outcome, and in-hospital mortality. Variables were entered into the initial regression model if the probability of their score statistic was <.05 and were removed if the probability was >.10. In all cases, a two-tailed *P* value <.05 was considered significant.

RESULTS

Characteristics of the study population at admission are shown in Table I. At admission, 38.0%, 27.0%, 31.1%, 21.8%, and 30.5% of the study population were being treated with β-blockers, diuretics, CCBs, ACE inhibitors, and ARBs, respectively, alone or in combination. Moreover, 9.9%, 0.8%, 7.5%, 3.5%, and 3.9% of the study population were receiving monotherapy with β-blockers, diuretics, CCBs, ACE inhibitors, and ARBs, respectively, and 24.7% were not receiving any antihypertensive agent.

At admission, the NIHSS score did not differ between patients who were receiving before-stroke monotherapy with β-blockers, diuretics, CCBs, ACE inhibitors, or ARBs and those who were not being treated with any antihypertensive agent (12.1±10.7, 2.5±1.3, 9.6±8.5, 10.4±10.3, 10.6±10.6, and 8.7±10.2, respectively; *P*=not significant [NS]). The NIHSS score was lower in patients who were being treated before stroke with diuretics (alone or in combination with other antihypertensive agents) than in those not treated with diuretics (6.5±6.7 and 9.4±9.6, respectively; *P*=.001). In contrast, the NIHSS did not differ between patients who were being treated before stroke with β-blockers (alone or in combination with other antihypertensive agents) and those who were not (8.4±8.8 and 8.7±9.2, respectively; *P*=NS), between patients treated before stroke with CCBs (alone or in combination with other antihypertensive agents) and those who were not (8.1±7.8 and 8.9±9.5, respectively; *P*=NS), between patients treated before stroke with ACE inhibitors (alone or in combination with other antihypertensive agents) and those who were not (8.0±8.2 and 8.8±9.3, respectively; *P*=NS), or between patients treated before stroke with ARBs (alone or in combination with other antihypertensive agents) and those who were not (8.1±8.3 and 8.8±9.3, respectively; *P*=NS).

TABLE I. Characteristics of the Study Population at Admission

Characteristic	Value
Age, y	78.8±6.7
Male, %	40.2
Systolic blood pressure, mm Hg	147±25
Diastolic blood pressure, mm Hg	81±13
Heart rate	79±15
Hypertension, %	81.7
Smoking (current/past), %	12.0/21.2
Package-years	15±35
Type 2 diabetes mellitus, %	32.2
Type 2 diabetes mellitus duration, y	10.3±8.4
Atrial fibrillation, %	35.9
Alcohol consumption, units per wk	1.6±9.7
Weight, kg	74.7±13.6
Body mass index, kg/m^2	27.5±5.1
Waist, cm	104±12
Waist/hip	0.98±0.07
Overweight/obese, %	40.4/25.6
Family history of cardiovascular disease, %	14.9
Coronary heart disease, %	27.6
Previous ischemic stroke, %	40.0
Chronic kidney disease, %	34.6
Chronic heart failure, %	19.7
Glucose, mg/dL	115±48
Low-density lipoprotein cholesterol, mg/dL	111±40
High-density lipoprotein cholesterol, mg/dL	46±15
Triglycerides, mg/dL	120±52
Uric acid, mg/dL	5.7±1.8
Estimated glomerular filtration rate, mL/min/1.73 m^2	69±23
Treatment before stroke with statins, %	27.2
Treatment before stroke with antiplatelet agents, %	39.8
Treatment before stroke with anticoagulants, %	11.4

Characteristics of patients with severe and nonsevere stroke are shown in Table II. Patients with severe stroke were older, more often women, had higher prevalence of atrial fibrillation, and less likely to be treated before stroke with diuretics. In binary logistic regression analysis, independent predictors of severe stroke were female sex (odds ratio [OR], 2.21; 95% confidence interval [CI], 1.23–3.96; *P*=.008) and atrial fibrillation (OR, 2.45; 95% CI, 1.42–4.19; *P*=.001). Treatment with diuretics before stroke was associated with nonsevere stroke (OR, 0.22; 95% CI, 0.09–0.51; *P*<.001).

At discharge, 64.3% of the study population had an adverse outcome. Characteristics of patients with adverse and favorable outcomes are shown in Table III.

TABLE II. Characteristics of Patients With Severe and Nonsevere Stroke

Characteristic	Patients With Severe Stroke (n=89)	Patients With Nonsevere Stroke (n=393)	*P* Value
Age, y	80.5±6.3	78.5±6.6	.023
Male, %	43.6	28.4	.023
Systolic blood pressure, mm Hg	145±26	146±24	.756
Diastolic blood pressure, mm Hg	82±15	80±13	.132
Heart rate	82±18	78±14	.065
Hypertension, %	75.7	82.2	.259
Smoking (current/past), %	10.8/17.6	13.2/22.7	.468
Package-years	10±23	17±39	.098
Type 2 diabetes mellitus, %	31.1	32.5	.920
Type 2 diabetes mellitus duration, y	10.0±6.9	10.9±8.6	.685
Atrial fibrillation, %	56.8	32.8	<.001
Alcohol consumption, units per wk	2.8±20.3	1.4±3.9	.560
Weight, kg	72.7±15.1	76.1±13.4	.171
Body mass index, kg/m^2	27.2±6.6	27.7±4.9	.665
Waist, cm	94±6	105±12	.211
Waist/hip	1.01±0.09	0.98±0.07	.098
Overweight/obese, %	18.8/43.8	41.3/31.6	.051
Family history of cardiovascular disease, %	13.5	16.6	.638
Coronary heart disease, %	31.1	28.2	.727
Previous ischemic stroke, %	48.6	42.3	.390
Chronic kidney disease, %	36.7	37.5	1.000
Chronic heart failure, %	23.0	19.3	.584
Glucose, mg/dL	123±57	112±47	.114
Low-density lipoprotein cholesterol, mg/dL	106±41	112±40	.358
High-density lipoprotein cholesterol, mg/dL	48±20	45±14	.345
Triglycerides, mg/dL	121±45	124±52	.354
Uric acid, mg/dL	5.8±2.2	5.8±1.8	.856
Estimated glomerular filtration rate, mL/min/1.73 m^2	69±21	69±23	.977
Treatment before stroke with statins, %[a]	25.7	27.3	.889
Treatment before stroke with antiplatelet agents, %	37.8	41.4	.665
Treatment before stroke with anticoagulants, %	16.2	11.0	.299
Treatment before stroke with β-blockers, %[a]	41.9	37.4	.561
Treatment before stroke with diuretics, %[a]	12.2	30.1	.003
Treatment before stroke with CCBs, %[a]	21.6	32.8	.081
Treatment before stroke with ACE inhibitors, %[a]	16.2	23.6	.220
Treatment before stroke with ARBs, %[a]	28.4	30.1	.885

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers. [a]Alone or in combination with other antihypertensive agents.

Patients with an adverse outcome were older, had lower prevalence of hypertension and higher prevalence of previous ischemic stroke, and had higher NIHSS score and lower serum triglyceride levels at admission. Patients with adverse outcome were also less likely to be treated before stroke with statins, diuretics, or β-blockers. In binary logistic regression analysis, independent predictors of adverse outcome were older age (OR, 1.13; 95% CI, 1.05–1.22; *P*=.001), NIHSS at admission (OR, 1.52; 95% CI, 1.33–1.74; *P*<.001), and history of ischemic stroke (OR, 2.69; 95% CI, 1.18–6.15; *P*=.018).

During hospitalization, 9.5% of the study population died. Significant differences between patients who died during hospitalization and patients who were discharged as well as antihypertensive treatment in the two groups are shown in Table IV. Patients who died during hospitalization were older, had higher prevalence of atrial fibrillation, and had higher NIHSS, DBP, and heart rate at admission. Antihypertensive treatment before stroke did not differ between patients who died during hospitalization and those discharged (Table III). In binary logistic regression analysis, independent predictors of in-hospital mortality were higher DBP at admission (OR, 1.09; 95% CI, 1.05–1.13; *P*<.001), higher NIHSS score at admission (OR, 1.19; 95% CI, 1.14–1.26; *P*<.001), and the presence of atrial fibrillation (OR, 2.81; 95% CI, 1.07–7.43; *P*=.037).

Because of the small number of patients on antihypertensive monotherapy, we analyzed as a group the patients who were treated with β-blockers only (n=48), diuretics only (n=4), or β-blockers in combination with diuretics (n=8). Stroke severity and outcome did not differ between this group (N=60) and patients who were

TABLE III. Characteristics of Patients With Adverse and Favorable Outcome

Characteristic	Patients With Adverse Outcome (n=310)	Patients With Favorable Outcome (n=172)	*P* Value
Age, y	80.2±6.6	76.7±6.4	<.001
Male, %	38.6	41.4	.640
Systolic blood pressure, mm Hg	146±26	150±23	.110
Diastolic blood pressure, mm Hg	82±14	81±12	.761
Heart rate	81±16	77±14	.124
Hypertension, %	77.3	87.0	.018
Smoking, (current/past), %	12.0/18.7	10.1/29.0	.052
Package-years	12±32	17±36	.205
Type 2 diabetes mellitus, %	34.3	30.8	.521
Type 2 diabetes mellitus duration, y	10.2±7.5	11.4±8.9	.437
Atrial fibrillation, %	39.0	33.1	.259
Alcohol consumption, units per wk	1.9±12.9	1.4±4.1	.598
Weight, kg	73.9±13.9	76.4±14.2	.123
Body mass index, kg/m^2	27.5±5.5	28.0±5.0	.390
Waist, cm	101±12	105±12	.126
Waist/hip	0.99±0.09	0.98±0.07	.589
Overweight/obese, %	37.5/35.9	39.8/30.9	.694
Family history of cardiovascular disease, %	15.5	16.0	1.000
Coronary heart disease, %	26.7	30.8	.425
Previous ischemic stroke, %	47.8	32.0	.002
Chronic kidney disease, %	40.7	32.7	.235
Chronic heart failure, %	19.5	19.5	1.000
National Institutes of Health Stroke Scale score at admission	12.6±9.4	2.2±2.5	<.001
Glucose, mg/dL	118±50	107±41	.054
Low-density lipoprotein cholesterol, mg/dL	107±41	117±42	.066
High-density lipoprotein cholesterol, mg/dL	46±16	47±14	.747
Triglycerides, mg/dL	110±43	132±58	.001
Uric acid, mg/dL	5.6±1.8	5.8±1.7	.329
Estimated glomerular filtration rate, mL/min/1.73 m^2	66±23	71±24	.105
Treatment before stroke with statins, %[a]	22.7	39.1	<.001
Treatment before stroke with antiplatelet agents, %	40.6	41.4	.953
Treatment before stroke with anticoagulants, %	12.0	13.0	.862
Treatment before stroke with β-blockers, %[a]	35.1	46.2	.029
Treatment before stroke with diuretics, %[a]	23.1	34.9	.011
Treatment before stroke with CCBs, %[a]	32.3	32.0	1.000
Treatment before stroke with ACE inhibitors, %[a]	21.5	23.1	.796
Treatment before stroke with ARBs, %[a]	28.3	36.7	.088

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers. [a]Alone or in combination with other antihypertensive agents.

not treated with either β-blockers or diuretics (data not shown). We also evaluated stroke severity and outcome in patients treated with diuretics in combination with either ACE inhibitors or ARBs (n=49) and in patients treated with CCBs in combination with either ACE inhibitors or ARBs (n=34). Neither stroke severity nor outcome differed between patients treated with these combinations and those who were not (data not shown).

DISCUSSION

The main finding of the present study is that treatment with diuretics before stroke is independently associated with less severe ischemic stroke. On the other hand, treatment with either diuretics or β-blockers before stroke was related to better functional outcome at discharge, but this association did not persist in multivariate analysis after adjusting for age, stroke severity, and history of ischemic stroke. Finally, treatment with CCBs, ACE inhibitors, or ARBs before stroke does not appear to affect either stroke severity or in-hospital outcome.

In the present study, pretreatment with β-blockers, either as monotherapy or in combination with other antihypertensive agents, was associated with reduced risk for adverse outcome in univariate analysis. This observation, however, was not confirmed in multivariate analysis when age, stroke severity, and history of stroke were considered. In contrast, previous studies did not report an association between pre-stroke use of β-blockers and outcome at discharge.[9,13,14] However,

TABLE IV. Significant Differences Between Patients Who Died During Hospitalization and Patients Discharged and Antihypertensive Treatment in the Two Groups

	Patients Who Died During Hospitalization (n=46)	Patients Who Were Discharged (n=436)	*P* Value
Age, y	81.5±7.2	78.6±6.7	.009
Atrial fibrillation, %	69.6	32.3	<.001
National Institutes of Health Stroke Scale score at admission	23.3±9.6	6.9±7.3	<.001
Diastolic blood pressure at admission, mm Hg	89±18	80±12	.003
Heart rate	89±16	78±15	<.001
Treatment before stroke with β-blockers, %[a]	39.1	37.8	.991
Treatment before stroke with diuretics, %[a]	15.2	28.2	.087
Treatment before stroke with CCBs, %[a]	28.3	31.4	.785
Treatment before stroke with ACE inhibitors, %[a]	19.6	22.0	.845
Treatment before stroke with ARBs, %[a]	23.9	31.2	.394

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers. [a]Alone or in combination with other antihypertensive agents.

one of the former studies used a different cutoff for adverse outcome (mRS ≥4),[14] the other evaluated outcome at 3 months after stroke,[13] whereas in the third a very small proportion of patients (9.9%) were receiving β-blockers.[9] A possible explanation for the potential benefit of treatment with β-blockers before stroke on stroke outcome is that these agents reduce heart rate. In turn, lower heart rate is associated with better stroke outcome.[17,18] Indeed, in our study, patients treated with β-blockers had lower heart rate (77±15 vs 80±15 in patients not treated with β-blockers; *P*=.048), and increased heart rate was associated with higher mortality risk in univariate analysis. However, this relationship did not persist in multivariate analysis. Despite the trend for a favorable effect of treatment with β-blockers before stroke on outcome, stoke severity was not affected by these agents, in agreement with previous studies.[9,13] However, an earlier small study (N=111) reported less severe stroke in patients who were taking β-blockers before stroke.[12] In contrast, a more recent and larger study (N=5568) reported more severe stroke in patients treated with β-blockers before stroke.[14] The use of different scales for evaluating stroke severity and the application of different cutoffs for defining severe stroke might explain these discrepant results. On the other hand, it should be mentioned that some trials showed that β-blockers are less effective in reducing the risk for stroke than CCBs or ARBs, despite similar reductions in blood pressure.[19,20]

Another important finding of the present study is that treatment with diuretics before ischemic stroke, alone or in combination with other antihypertensive drugs, was associated with better functional outcome at discharge in univariate analysis. This beneficial effect of diuretics appears to be mostly the result of a neuroprotective effect, since patients who were receiving diuretics before stroke had less severe stroke. Moreover, treatment with diuretics was not independently associated with favorable outcome when stroke severity was included in multivariate analysis. Diuretics increase the activity of the renin-angiotensin system and experimental data suggest that the activation of angiotensin II receptor type 2 receptors might increase cerebral blood flow, exert antioxidant effects, and reduce neuronal apoptosis.[21–24] In contrast to our findings, a previous study reported no effect of treatment with diuretics before stroke on stroke severity and outcome,[9] whereas another reported more severe stroke in patients who were taking diuretics before stroke.[10] However, the latter studies included patients with first-ever ischemic stroke only and primarily aimed to evaluate the effect of treatment with ACE inhibitors or ARBS before stroke on stroke severity.[9,10]

In agreement with most previous reports,[9,10] treatment with CCBs before stroke had no effect on stroke severity or outcome in our population. Only one study reported less severe stroke in patients who were taking CCBs before stroke.[14] However, the latter study used a different scale for the evaluation of stroke severity.[14] Moreover, no effect of CCBs on outcome at discharge or in-hospital mortality was observed.[14] In addition, the Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study suggested that nitrendipine is less effective than eprosartan in the secondary prevention of stroke despite a similar reduction in blood pressure.[25] On the other hand, some previous studies reported a favorable effect of treatment with ACE inhibitors[10,11] or ARBs[9] before stroke on stroke severity and short-term outcome. Experimental data suggest that ACE inhibitors and ARBs exert neuroprotective actions. These actions appear to be mediated by an anti-inflammatory effect and by the induction of vasodilation in the peripheral area of ischemia.[26–28] In contrast, we did not observe this beneficial effect of either ACE inhibitors or ARBs. Notably, most studies also did not report an association between pretreatment with ACE inhibitors[9,13,14] or ARBs[10,14] and stroke severity or outcome. Moreover, ARBs do not appear to affect cerebral blood flow.[29] Given these conflicting results, it remains unclear whether ACE inhibitors or ARBs exert neuroprotective effects in patients who experience an acute ischemic stroke.

CONCLUSIONS

Our study suggests that treatment with diuretics before stroke is independently related to less severe stroke.

Pre-stroke use of either diuretics or β-blockers was also associated with better functional outcome at discharge, but this benefit did not persist in multivariate analysis. The other major classes of antihypertensive agents, ie, CCBs, ACE inhibitors, and ARBs, do not appear to affect either stroke severity or outcome. These findings highlight the important role of diuretics in the management of hypertension and the prevention of target organ damage, particularly cerebrovascular disease.

Disclosures: The authors report no specific funding in relation to this research and no conflicts of interest to disclose.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6–e245.
2. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:517–584.
3. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke*. 2014;45:2160–2236.
4. 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*. 2003;362:1527–1535.
5. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
6. Herttua K, Tabak AG, Martikainen P, et al. Adherence to antihypertensive therapy prior to the first presentation of stroke in hypertensive adults: population-based study. *Eur Heart J*. 2013;34:2933–2939.
7. Xu J, Zhao X, Wang Y, et al. Impact of a better persistence with antihypertensive agents on ischemic stroke outcomes for secondary prevention. *PLoS One*. 2013;8:e65233.
8. Ravenni R, Jabre JF, Casiglia E, Mazza A. Primary stroke prevention and hypertension treatment: which is the first-line strategy? *Neurol Int*. 2011;3:e12.
9. Fuentes B, Fernandez-Dominguez J, Ortega-Casarrubios MA, et al. Treatment with angiotensin receptor blockers before stroke could exert a favourable effect in acute cerebral infarction. *J Hypertens*. 2010;28:575–581.
10. Chitravas N, Dewey HM, Nicol MB, et al. Is prestroke use of angiotensin-converting enzyme inhibitors associated with better outcome? *Neurology*. 2007;68:1687–1693.
11. Selim M, Savitz S, Linfante I, et al. Effect of pre-stroke use of ACE inhibitors on ischemic stroke severity. *BMC Neurology*. 2005;5:10.
12. Laowattana S, Oppenheimer SM. Protective effects of beta-blockers in cerebrovascular disease. *Neurology*. 2007;68:509–514.
13. De Raedt S, Haentjens P, De Smedt E, et al. Pre-stroke use of beta-blockers does not affect ischaemic stroke severity and outcome. *Eur J Neurol*. 2012;19:234–240.
14. Dowlatshahi D, Hakim A, Fang J, Sharma M. Pre admission antithrombotics are associated with improved outcomes following ischaemic stroke: a cohort from the Registry of the Canadian Stroke Network. *Int J Stroke*. 2009;4:328–334.
15. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972; 18:499–502.
16. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461–470.
17. Tomii Y, Toyoda K, Suzuki R, et al. Effects of 24-hour blood pressure and heart rate recorded with ambulatory blood pressure monitoring on recovery from acute ischemic stroke. *Stroke*. 2011;42: 3511–3517.
18. Bohm M, Cotton D, Foster L, et al. Impact of resting heart rate on mortality, disability and cognitive decline in patients after ischaemic stroke. *Eur Heart J*. 2012;33:2804–2812.
19. Dahlöf B, Devereux RB, Kjeldsen SE, et al. 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.
20. Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.
21. Fernandez LA, Caride VJ, Strömberg C, et al. Angiotensin AT2 receptor stimulation increases survival in gerbils with abrupt unilateral carotid ligation. *J Cardiovasc Pharmacol*. 1994;24:937–940.
22. Makino I, Shibata K, Ohgami Y, et al. Transient upregulation of the AT2 receptor mRNA level after global ischemia in the rat brain. *Neuropeptides*. 1996;30:596–601.
23. Dalmay F, Mazouz H, Allard J, et al. Non-AT(1)-receptor-mediated protective effect of angiotensin against acute ischaemic stroke in the gerbil. *J Renin Angiotensin Aldosterone Syst*. 2001;2:103–106.
24. Iwai M, Liu HW, Chen R, et al. Possible inhibition of focal cerebral ischemia by angiotensin II type 2 receptor stimulation. *Circulation*. 2004;110:843–848.
25. Schrader J, Lüders S, Kulschewski A, et al. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke*. 2005;36:1218–1226.
26. Sironi L, Gelosa P, Guerrini U, et al. Anti-inflammatory effects of AT1 receptor blockade provide end-organ protection in stroke-prone rats independently from blood pressure fall. *J Pharmacol Exp Ther*. 2004;311:989–995.
27. Ito T, Nishimura Y, Saavedra J. Pre-treatment with candesartan protects from cerebral ischaemia. *J Renin Angiotensin Aldosterone Syst*. 2001;2:174–179.
28. Ito T, Yamakawa H, Bregonzio C, et al. Protection against ischemia and improvement of cerebral blood flow in genetically hypertensive rats by chronic pretreatment with an angiotensin II AT1 antagonist. *Stroke*. 2002;33:2297–2303.
29. Périard D, Rey MA, Casagrande D, et al. The effect of valsartan versus non-RAAS treatment on autoregulation of cerebral blood flow. *Cerebrovasc Dis*. 2012;34:78–85.