Pulse Pressure and Cognitive Decline in Stroke Patients With White Matter Changes

Zhaolu Wang, MD;[1] Adrian Wong, PhD;[1] Wenyan Liu, MD;[1] Jie Yang, MD, PhD;[2] Winnie C.W. Chu, MD;[3] Lisa Au, MD;[1] Alexander Lau, MD;[1] Yunyun Xiong, MD, PhD;[4] Vincent C.T. Mok, MD[1]

From the Department of Medicine and Therapeutics, Lui Che Woo Institute of Innovative Medicine, The Chinese University of Hong Kong, Hong Kong ;[1] Key Laboratory of Neurogenetics and Channelopathies of Guangdong Province and the Ministry of Education of China, Institute of Neuroscience and the Second Affiliated Hospital of Guangzhou Medical University, Guangzhou;[2] Department of Imaging and Interventional Radiology, Lui Che Woo Institute of Innovative Medicine, The Chinese University of Hong Kong, Hong Kong;[3] and Department of Neurology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China[4]

The authors hypothesized that both high and low pulse pressure (PP) may predict cognitive decline in stroke/transient ischemic attack (TIA) patients with white matter changes (WMCs). The authors prospectively followed up 406 ischemic stroke/TIA patients with confluent WMCs over 18 months. PP was measured at 3 to 6 months after stroke/TIA and categorized into four groups by quartile. Cognition was assessed 3 to 6 months and 15 to 18 months after stroke/TIA using the Clinical Dementia Rating and Mini-Mental State Examination (MMSE). Logistic regression showed that patients in the first quartile of PP had a 5.9-fold higher risk for developing cognitive decline than patients in the third quartile (odds ratio, 5.9; 95% confidence interval, 1.7–20.6), while patients in the fourth quartile had a 3.5-fold higher risk for cognitive decline than those in the third quartile (odds ratio, 3.5; 95% confidence interval, 1.0–12.4). This U-shaped relationship was also evident between PP and cognitive decline in MMSE, underlining the role of arterial stiffness and hypoperfusion in cognitive decline related to small vessel disease. *J Clin Hypertens (Greenwich).* 2015;17:694–698. © 2015 Wiley Periodicals, Inc.

Presence of white matter changes (WMCs) significantly increases future risk of cognitive decline. Our recent study showed that among patients with WMC, one third experienced cognitive decline and one fifth developed incident dementia over a 2-year period despite optimal control of traditional vascular risk factors.[1] Mechanisms explaining cognitive decline associated with WMCs are not fully understood and are probably complex. Studies suggest that progressing WMCs and related brain atrophy play an important role.[2] Age and high blood pressure (BP) are generally regarded as the most important risk factors for the development of WMC. However, the Rotterdam Scan Study shows that high systolic BP or diastolic BP accounts mainly for the initial evolution of WMCs, and association between systolic or diastolic BP increase and WMC progression becomes insignificant in those with severe WMCs at baseline.[3] Other factors may explain WMC progression and/or the related cognitive decline in patients with severe WMCs.

A recent cross-sectional study shows that among healthy elderly individuals, high pulse pressure (PP; the difference between systolic BP and diastolic BP) is associated with severe WMCs independent of individual BP levels.[4] High PP in older people is a marker of increased large artery stiffness and widespread atherosclerosis.[5,6] PP may also be related to cognitive functions. A longitudinal study showed that both high and low levels of PP were predictive of incident dementia among dementia/stroke-free patients.[7] Poor cerebral perfusion associated with reduced cardiac output as indexed by low PP may account for the association between low PP and increased risk of dementia.[7–9] It is therefore biologically plausible to hypothesize that extremes of PP may predict cognitive decline in patients with WMC as well. In the present study, we prospectively tested this hypothesis among patients with ischemic stroke or transient ischemic attack (TIA) with confluent WMCs over a 15- to 18-month follow-up period. Understanding the mechanism of WMC-related cognitive decline may shed light on preventive strategies.

METHODS

Patients

Participants were patients from the ongoing Stroke Registry Investigating Cognitive Decline (STRIDE) study. The STRIDE study recruited 1013 consecutive acute stroke (ischemic and hemorrhagic)/TIA patients admitted to Prince of Wales Hospital, Hong Kong, between 2009 and 2010, aiming to investigate the rate and mechanisms of cognitive decline over a 5-year period. The details of the STRIDE trial have been described previously.[10] In this study, we included 406 ischemic stroke/TIA patients with confluent WMCs on computed tomography (CT) or magnetic resonance imaging (MRI) at baseline from the STRIDE study. Confluent WMC was defined as a score of ≥2 on the

Address for correspondence: Adrian Wong, PhD, Department of Medicine and Therapeutics, 10/F Clinical Sciences Building, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China
E-mail: adrianwong@cuhk.edu.hk

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age-related white matter changes (ARWMCs) scale in at least one brain region.[1,11] We included patients with confluent WMCs but not punctuate lesions because pathological studies show that early confluent to confluent lesions are likely to represent true ischemic lesions associated with cerebral small vessel disease while punctate lesions on MRI are commonly of nonischemic origin.[12] We excluded those with a known history of dementia, which was diagnosed by a neurologist specialized in dementia (VCTM, LA) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, as previously described.[10] This study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics committee, and written informed consent was obtained from each participant.

Demographic and Vascular Risk Factors

We collected data on basic demography (age, sex, education in years) and vascular risk factors at 3 to 6 months after stroke/TIA. Diabetes mellitus [DM] was defined as a fasting serum glucose level of ≥7.0 mmol/L, a postprandial serum glucose level of ≥11.1 mmol/L, or the use of oral hypoglycemic agents/insulin. Hyperlipidemia was defined as a total cholesterol level of ≥5.2 mmol/L, a low-density lipoprotein cholesterol level of ≥2.6 mmol/L, a triglyceride level of ≥1.70 mmol/L, or the use of lipid-lowering drugs. Smoking/alcohol intake was dichotomized as ever or never smoked and ever or never drank alcohol, respectively. Atrial fibrillation (AF) and congestive heart failure (CHF) were recorded. Recurrent strokes (including hemorrhagic and ischemic strokes and subarachnoid hemorrhage) were recorded during follow-up. The National Institutes of Health Stroke Scale (NIHSS) was used to quantify stroke severity on admission. Antihypertensive therapy including diuretics, β-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blockers on discharge was recorded.

BP Measurements and Neuropsychological Assessments

Both systolic BP and diastolic BP were measured three times by trained research assistants at the right brachial artery after a 10-minute rest in a sitting position at 3 to 6 months after stroke/TIA. The average value taken from these three PP measures were obtained for each patient and further divided into quartiles for statistical analyses, respectively. Cognition was assessed at 3 to 6 months and at 15 to 18 months after stroke/TIA using the Clinical Dementia Rating (CDR) global score[13] and the total score of the Mini-Mental State Examination (MMSE). Cognitive decline was defined as at least one grading increase in CDR or at least a three-point decrease in MMSE between baseline and follow-up.[14–16]

Neuroimaging Examinations

Noncontrast brain CT was performed with a multidetector row clinical CT scanner for all patients upon arrival to the accident and emergency department. Brain MRI (1.5T scanner, Sonata; Siemens Medical, Erlangen, Germany, or 3.0T scanner, Achieva 3.0T TX Series; Philips Medical System, Best, The Netherlands) was performed in patients for whom we were unable to classify the stroke subtypes based on CT and other clinical parameters. For patients who had both CT and MRI, ratings were performed only on MRI. Among 406 patients recruited in this study, MRI was performed in 222 patients. The severity of WMCs was rated on axial fluid-attenuated inversion recovery or CT scan using ARWMC scale.[11] Only patients with confluent WMCs were analyzed in this study. We used ventricular-brain ratio (VBR) to index global or subcortical atrophy. The VBR was calculated as the mean of the biventricular width at the level of the frontal and occipital horns and at the level of the body of the caudate nuclei divided by the corresponding brain width at those levels on either MRI or CT.[17] Medial temporal lobe atrophy (MTLA) was rated on coronal images on T1-weighted MRI or CT oblique coronal reconstructed images using the Scheltens' 5-point (0–4) scale.[18] The more severe MTLA rating of the two hemispheres was used as the total MTLA score for analysis. Presence of old lacunes was also recorded. All ratings were performed blind to patients' clinical data. To investigate whether the visual rating methods for WMC, old lacunes, VBR, and MTLA are applicable to both CT and MRI, we performed intermodality agreement between CT and MRI based on a random selection of 30 scans. Agreements for WMC (intraclass correlation coefficient [ICC] 0.82), VBR (ICC 0.85), left MTLA (ICC 0.86), and lacunes (ICC 0.82) were excellent. Agreement for right MTLA (ICC 0.58) was acceptable. Intrarater agreement for a single rater in rating WMC, VBR, MTLA, and lacunes was excellent for both CT and MRI (ICC >0.9). Interrater agreements for WMC, VBR, MTLA, and lacunes varied from good to excellent for CT (ICC 0.85–0.99) and MRI (ICC 0.75–0.93).

Statistics

Binary logistic regression was used to examine the association between PP (independent variable) and cognitive decline (dependent variable). To examine the presence of a U-shaped association (nonlinear) between PP with cognitive decline, PP was categorized into quartiles and entered the model as a categorical variable.[19–21] Cognitive decline was indexed by CDR and MMSE changes, respectively. Putative confounding factors, including baseline age, sex, education, DM, hyperlipidemia, smoking, alcohol, AF or CHF, recurrent stroke, VBR, MTLA, lacunes,[22] antihypertensive therapy on discharge, and admission NIHSS score were first examined in a series of exploratory univariable models, and only variables with $P<.10$ in univariable models were then entered into multivariate regression models. Since age and education are potential confounding factors for cognition, these two factors are also put into the model for further adjustments, no matter whether they had a $P<.10$

in univariable models. Variance inflation factor (VIF) was calculated and a VIF >2.5 indicated a multicollinearity problem in predictor variables.[23] SPSS 16.0 (SPSS Inc, IBM, Armonk, NY) was used and an α value was set at 0.05 for all statistical analyses.

RESULTS

Among the 406 patients with confluent WMCs, baseline CDR and MMSE were available in 378 (93.1%) and 404 (99.5%), respectively. The demographic, clinical, and imaging characteristics of the patients at baseline are summarized in Table I. Due to death, dropout, or patients' inability to complete the entire neuropsychological assessments, CDR and MMSE were available in 289 (76.5%) and 313 (77.5%) patients at 15 to 18 months of follow-up, respectively. Cognitive decline was observed in 44 and 73 patients at 15 to 18 months, as indexed by CDR or MMSE, respectively. Compared with patients with follow-up assessments, those without follow-up assessments had a higher CDR score or lower MMSE score at baseline, indicating worse baseline cognitive function (data not shown). No other baseline difference was found between patients with and without follow-up assessments.

Table II shows the relationship between PP levels and cognitive decline. As indexed by CDR, univariable logistic model showed that patients in the third quartile of PP had a significantly smaller crude odds ratio (OR) for cognitive decline compared with that in the first quartile (OR=0.3, *P*=.016; Quartile cutoff points were 56.0 mm Hg, 70.7 mm Hg, and 87.0 mm Hg, respectively). Since the third quartile had the smallest OR, it was then chosen as a reference in the multivariable regression model to better test the U-shaped association. After adjusting for age, education, baseline CDR score, and MTLA (whose *P* values were <.1 in the initial univariable models), patients in the first or fourth quartile of PP had significantly higher risk of cognitive decline, compared with patients in the third quartile (OR=5.9, *P*=.006, for the first quartile and OR=3.5, *P*=.049 for the fourth quartile; Table II). Further adjustment for ARWMC total score, recurrent stroke, diastolic BP, AF or CHF, admission NIHSS score, and antihypertensive therapy on discharge in the multivariable model did not change this association (OR=6.2, 95% confidence interval [CI], 1.6–24.3, *P*=.009, first vs third; OR=4.2; 95% CI, 1.1–16.5, *P*=.038, fourth vs third; systolic BP was not included in this multivariable model because of collinearity with PP). The significantly higher OR in the first and fourth quartiles indicated a U-curve association between PP and the risk of cognitive decline indexed by CDR, with the lowest risk at the third quartile.

A U-shaped association was also found between PP and cognitive decline indexed by MMSE (Table II). The third quartile had a smaller crude OR than that of the first quartile in the univariable model (Quartile cutoff points were 56.0 mm Hg, 71.0 mm Hg, and 87.0 mm Hg, respectively). After adjustments for age, VBR, and

TABLE I. Characteristics of the Patients at Baseline

Characteristics	Values (n=406)
Demographics	
Age, y, mean (SD)	74.8 (9.6)
Men, No. (%)	228 (56.2)
Education (range), y	4.0 (0–30)
Clinical characteristics	
Diabetes mellitus, No. (%)	160 (39.4)
Hyperlipidimia, No. (%)	248 (61.1.)
Smoking, No. (%)	167 (41.1)
Alcohol, No. (%)	49 (12.1)
AF or CHF	70 (17.2)
Systolic BP, mean (SD)	153.6 (22.7)
Diastolic BP, mean (SD)	81.9 (12.4)
PP, mean (SD)	71.6 (20.8)
Global CDR, 0/0.5/1/2/3[a]	169/141/28/24/16
Total MMSE, mean (SD)[b]	21.9 (6.8)
Admission NIHSS, mean (SD)	5.24 (5.31)
Antihypertensive therapy, No. (%)	116 (28.6)
MRI findings	
VBR, mean (SD)	0.33 (0.05)
Lacunes, No. (%)	317 (78.1)
MTLA, 0/1/2/3/4	72/136/97/65/36

Abbreviations: AF, atrial fibrillation; BP, blood pressure; CDR, clinical dementia rating scale; CHF, congestive heart failure; MMSE, mini-mental state examination; MTLA, medial temporal lobe atrophy; SD, standard deviation; VBR, ventricular brain ratio. [a]n=378 for global CDR; [b]n=404 for total MMSE due to unavailable cognitive assessments.

TABLE II. Relationship Between PP and Cognitive Decline in CDR or MMSE

	Crude[a]		Adjusted[b,c]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
PP and CDR				
First	1		5.9 (1.7–20.6)	.006
Second	0.6 (0.3–1.4)	.257	2.9 (0.8–10.3)	.103
Third	0.3 (0.1–0.8)	.016	1	
Fourth	0.6 (0.3–1.5)	.325	3.5 (1.0–12.4)	.049
PP and MMSE				
First	1		2.7 (1.1–6.6)	.034
Second	0.9 (0.4–1.8)	.679	2.0 (0.9–4.9)	.110
Third	0.4 (0.2–1.0)	.044	1	
Fourth	1.4 (0.7–2.8)	.360	3.3 (1.4–7.7)	.005

Abbreviations: CDR, clinical dementia rating scale; CI, confidence interval; MMSE, mini-mental state examination; MTLA, medial temporal lobe atrophy; OR, odds ratio; PP, pulse pressure; VBR, ventricular brain ratio. First, second, third, and fourth refer to the four quartile groups of PP levels, from low (first) to high (fourth). For PP in CDR, quartile cutoff points were 56.0 mm Hg, 70.7 mm Hg, and 87.0 mm Hg, respectively. PP in MMSE were were 56.0 mm Hg, 71.0 mm Hg, and 87.0 mm Hg, respectively. [a]The first quartile is used as a reference. [b]The third quartile is used as a reference. [c]Adjustments for baseline CDR score, MTLA, age, and education (for PP and CDR). Adjustments for age, VBR, and education (for PP and MMSE).

education (whose *P* values were <.1 in univariable screen), both the patients in the first and fourth quartiles had significantly higher ORs than those in the third quartile (OR=2.7, *P*=.034, first vs third; OR=3.3, *P*=.005, fourth vs third). Further adjustment for ARWMC total score, recurrent stroke, diastolic BP, baseline cognitive function, AF or CHF, admission NIHSS score and antihypertensive therapy on discharge did not affect the association (OR=2.3, 95% CI, 1.0–5.5, *P*=.063, first vs third; OR=2.6, 95% CI, 1.1–6.1, *P*=.030, fourth vs third; systolic BP was not included in this multivariable model because of collinearity with PP).

In addition, we also analyzed the relationship between systolic or diastolic BP and cognitive decline using the same statistical methods as above. Only low systolic BP was associated with cognitive decline as indexed by CDR after adjusting for age, education, baseline CDR score, and MTLA (OR=3.7, *P*=.010, first vs third). No relationship was found between diastolic BP and cognitive decline indexed by CDR. Neither systolic nor diastolic BP was associated with cognitive decline indexed by MMSE. Moreover, we did not observe any association between PP and cognitive decline among patients without confluent WMCs (n=619, data not shown).

DISCUSSION

In this study we found a U-shaped relationship between PP levels and cognitive decline in ischemic stroke patients with confluent WMCs. This relationship was independent of age, atrophy, and other confounding factors.

Our findings concur with that of another study among stroke/dementia-free patients.[7] Increased PP is a marker of increased arterial stiffness or atherosclerosis in large conduit arteries.[5,6] As a result of the reduced damping of arterial waveform, large arterial stiffening exposes blood vessels, especially the small vessels in the brain, to highly pulsatile pressure and blood flow, which probably contribute to the pathogenesis and progression of cerebral small vessel disease,[24,25] resulting in WMC development and progression.[4,26] Hence, our study suggests the important role of large arterial stiffness in cognitive decline associated with cerebral small vessel disease (ie, cross-talk between large arteries and cerebral small vessels).[24,27,28]

By contrast, mechanisms underlying the relationship between low PP and cognition are different. In addition to arterial compliance, PP also depends on left ventricular ejection and stroke volume.[29,30] Low PP may indicate decreased blood ejection and stroke volume that may reduce cerebral blood flow and contribute to cognitive decline.[8,9] Heart failure, AF, and orthostatic hypotension were all observed to be related to the presence of WMC.[31] It is thus possible that patients with low or high PP may develop more WMCs that further impaired cognition during follow-up.[4,24–26,31,32] However, this hypothesis could not be tested in our study as imaging was not repeated at follow-up.

Our study implies that PP may be a better predictor of cognitive decline as compared with systolic BP or diastolic BP. Several large outcome trials showed that PP was a stronger risk factor for cardiovascular events than other BP parameters.[33–35] The Framingham study showed that with increasing age, there was a gradual shift of contribution from diastolic BP to systolic BP and eventually to PP in predicting chronic heart disease.[36] The Rotterdam study showed that increased systolic or diastolic BP only contributed to WMC progression in patients without severe WMCs at baseline and in young patients but not in patients with severe WMCs at baseline or in patients who were very old.[3] Our finding suggested that PP, instead of systolic/diastolic BP, may contibute to WMC progression and related cogntive decline. In addition, this U-shaped association was only observed in patients with confluent WMCs but not in patients without confluent WMCs, indicating that patients with confluent WMCs are more vulnerable to PP fluctuation and related cognitive dysfunction. Previous studies have shown increased cerebrovascular resistance/pulsatility and impaired autoregulation of cerebral blood flow in patients with severe WMCs compared with those without,[25,37] which may account for the exclusive U-shaped association in patients with confluent WMCs. It is therefore important to identify patients with severe WMCs with imparied PP to prevent cognitive decline.

STUDY STRENGTHS AND LIMITATIONS

The strength of this study is that we longitudinally investigated a large sample of stroke patients with WMCs. We also adjusted for several confounding factors including brain atrophy. However, an even larger sample size is needed to categorize PP into more groups (eg, every 10-mm Hg increment) in order to get a detailed relationship between PP and cognitive decline (how the risk of cognitive decline fluctuates as PP goes up and down). There are several limitations in our study. First, around 23% of patients were lost to follow-up. Since patients lost to follow-up were more cognitively impaired at baseline compared with those who were included in the final analysis, our results might not be generalized to patients with more impaired cognitive function. Second, as the results are based on patients with stroke or TIA, our findings might not apply to the entire spectrum of patients with confluent WMCs, eg, among those without stroke or TIA. Third, although this study had a longitudinal design, BP data on follow-up were not available and they did not allow interpretation of causality in mechanisms explaining the relationships between PP, WMCs, and cognitive decline. For management, further studies are needed to investigate whether proper control of PP such as lifestyle changes,[38] folic acid,[39] and neuroendocrine-directed therapies[38] may retard cognitive decline in persons with confluent WMCs.

CONCLUSIONS

A U-shaped relationship existed between baseline PP and cognitive decline in ischemic stroke/TIA patients

with WMCs, suggesting an important role of large arterial stiffness and hypoperfusion in cognitive decline related to small vessel disease. Findings from our study provide new targets for preventing the cognitive decline associated with WMCs.

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References

1. Mok V, Xiong Y, Wong KK, et al. Predictors for cognitive decline in patients with confluent white matter hyperintensities. *Alzheimers Dement*. 2012;8:S96–S103.
2. Schmidt R, Petrovic K, Ropele S, et al. Progression of leukoaraiosis and cognition. *Stroke*. 2007;38:2619–2625.
3. van Dijk EJ, Prins ND, Vrooman HA, et al. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke*. 2008;39:2712–2719.
4. Kim CK, Lee SH, Kim BJ, et al. Age-independent association of pulse pressure with cerebral white matter lesions in asymptomatic elderly individuals. *J Hypertens*. 2011;29:325–329.
5. Safar ME. Pulse pressure in essential hypertension: clinical and therapeutical implications. *J Hypertens*. 1989;7:769–776.
6. Safar ME, Siche JP, Mallion JM, et al. Arterial mechanics predict cardiovascular risk in hypertension. *J Hypertens*. 1997;15:1605–1611.
7. Qiu C, Winblad B, Viitanen M, et al. Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. *Stroke*. 2003;34:594–599.
8. Zuccala G, Onder G, Pedone C, et al. Hypotension and cognitive impairment: selective association in patients with heart failure. *Neurology*. 2001;57:1986–1992.
9. de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. *Stroke*. 2002;33:1152–1162.
10. Yang J, Wong A, Wang Z, et al. Risk factors for incident dementia after stroke and transient ischemic attack. *Alzheimers Dement*. 2015;11:16–23.
11. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318–1322.
12. Schmidt R, Schmidt H, Haybaeck J, et al. Heterogeneity in age-related white matter changes. *Acta Neuropathol*. 2011;122:171–185.
13. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43:2412–2414.
14. Hensel A, Angermeyer MC, Riedel-Heller SG. Measuring cognitive change in older adults: reliable change indices for the Mini-Mental State Examination. *J Neurol Neurosurg Psychiatry*. 2007;78:1298–1303.
15. Yaffe K, Lui LY, Grady D, et al. Cognitive decline in women in relation to non-protein-bound oestradiol concentrations. *Lancet*. 2000;356:708–712.
16. Rist PM, Chalmers J, Arima H, et al. Baseline cognitive function, recurrent stroke, and risk of dementia in patients with stroke. *Stroke*. 2013;44:1790–1795.
17. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol*. 2000;47:145–151.
18. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry*. 1992;55:967–972.
19. Onat A, Can G, Ademoglu E, et al. Coronary disease risk curve of serum creatinine is linear in Turkish men. U-shaped in women. *J Investig Med*. 2013;61:27–33.
20. Makita S, Onoda T, Ohsawa M, et al. Influence of mild-to-moderate alcohol consumption on cardiovascular diseases in men from the general population. *Atherosclerosis*. 2012;224:222–227.
21. Bangalore S, Qin J, Sloan S, et al. What is the optimal blood pressure in patients after acute coronary syndromes?: relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. *Circulation*. 2010;122:2142–2151.
22. Brainin M, Tuomilehto J, Heiss WD, et al. Post-stroke cognitive decline: an update and perspectives for clinical research. *Eur J Neurol*. 2015;22:229–238, e13-6.
23. Allison PD. *Logistic Regression Using the SAS System: Theory and Application*. Cary, NC: SAS Press; 1999.
24. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension*. 2005;46:200–204.
25. Webb AJ, Simoni M, Mazzucco S, et al. Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. *Stroke*. 2012;43:2631–2636.
26. Poels MM, Zaccai K, Verwoert GC, et al. Arterial stiffness and cerebral small vessel disease: the Rotterdam Scan Study. *Stroke*. 2012;43:2637–2642.
27. Scuteri A, Brancati AM, Gianni W, et al. Arterial stiffness is an independent risk factor for cognitive impairment in the elderly: a pilot study. *J Hypertens*. 2005;23:1211–1216.
28. Xu WH. Large artery: an important target for cerebral small vessel diseases. *Ann Transl Med*. 2014;2:78.
29. Franklin SS, Khan SA, Wong ND, et al. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. *Circulation*. 1999;100:354–360.
30. Domanski MJ, Davis BR, Pfeffer MA, et al. Isolated systolic hypertension: prognostic information provided by pulse pressure. *Hypertension*. 1999;34:375–380.
31. Raiha I, Tarvonen S, Kurki T, et al. Relationship between vascular factors and white matter low attenuation of the brain. *Acta Neurol Scand*. 1993;87:286–289.
32. Peng J, Lu F, Wang Z, et al. Excessive lowering of blood pressure is not beneficial for progression of brain white matter hyperintensive and cognitive impairment in elderly hypertensive patients: 4-year follow-up study. *J Am Med Dir Assoc*. 2014;15:904–910.
33. Millar JA, Lever AF, Burke V. Pulse pressure as a risk factor for cardiovascular events in the MRC Mild Hypertension Trial. *J Hypertens*. 1999;17:1065–1072.
34. Blacher J, Staessen JA, Girerd X, et al. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch Intern Med*. 2000;160:1085–1089.
35. Fernandez-Fresnedo G, Rodrigo E, de Francisco AL, et al. Role of pulse pressure on cardiovascular risk in chronic kidney disease patients. *J Am Soc Nephrol*. 2006;17:S246–S249.
36. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation*. 2001;103:1245–1249.
37. Matsushita K, Kuriyama Y, Nagatsuka K, et al. Periventricular white matter lucency and cerebral blood flow autoregulation in hypertensive patients. *Hypertension*. 1994;23:565–568.
38. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol*. 2005;25:932–943.
39. Williams C, Kingwell BA, Burke K, et al. Folic acid supplementation for 3 wk reduces pulse pressure and large artery stiffness independent of MTHFR genotype. *Am J Clin Nutr*. 2005;82:26–31.