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Original Article

The correlation of homocysteine and inflammation level with cerebral infarction in hypertensive patients

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Abstract: Objective: This study aimed to explore the correlation of Homocysteine (Hcy) and inflammation level with cerebral infarction (CI) in hypertensive patients. Methods: A total of 122 hypertensive patients were selected from our hospital as the objects of the study and divided into stroke group (SG, n=51) and non-stroke group (NSG, n=71) according to whether they were diagnosed with CI. Besides, 50 healthy individuals were selected and included in control group (CG). Hcy, total cholesterol (TC), triacylglycerol (TG), low density lipoprotein cholesterol (LDL-C), tumor necrosis factor-α (TNF-α), C-reaction protein (CRP) and interleukin-6 (IL-6) were detected and compared among the three groups. Active treatment and follow-up visit were provided for SG to compare the changes of Hcy, TNF-α and scores for National Institutes of Health Stroke Scale (NIHSS) before treatment and at 1, 3 and 6 months after treatment. The last part was an analysis on correlation of Hcy, TNF-α, IL-6 and CRP with hypertensive cerebral infarction (HCI). Results: The levels of Hcy, TC, TG, LDL-C, TNF-α, IL-6 and CRP in SG were higher than those in NSG and CG, and those of NSG were higher than those of CG, showing statistically significant difference between groups (P<0.05). Hcy, TNF-α and NHISS scores of SG were reduced significantly after treatment, indicating significant difference compared with those before treatment (P<0.05). Conclusion: The levels of Hcy and inflammatory factors were positively correlated with CI incidence in hypertensive patients. The hypertensive patients with abnormally higher laboratory indices mentioned above should be treated actively to prevent CI and thus improve prognosis.

Keywords: Homocysteine, inflammation level, hypertension, cerebral infarction, correlation

Introduction

According to researches, cardiovascular and cerebrovascular diseases are not only the leading cause of death in the world, but also the major issue of public health at present. The investigation conducted in 2004 indicated that about 17 million people died of cardiovascular and cerebrovascular diseases worldwide, accounting for about 29% of deaths due to diseases. Thereinto, 7 million people died of coronary heart disease and 6 million died of stroke. As predicted by World Health Organization, 23 million people will die of cardiovascular and cerebrovascular diseases around the world by 2030 [1-3]. In recent years, with the emergence of social aging and the changes of dietary structure in China, the prevalence of coronary heart disease, myocardial infarction, stroke and other cardiovascular and cerebrovascular diseases has gradually increased [4, 5]. Hypertension is a clinical syndrome characterized by abnormal increase of blood pressure and complicated with multiorgan dysfunction or organic injury in heart, brain, kidney, *etc*. Besides, it is the most common chronic disease at present and also the risk factor of various cardiovascular and cerebrovascular diseases [6, 7]. According to an epidemiological investigation of hypertension, more than 25% adults currently suffer from hypertension worldwide, and this figure is expected to reach 29% by 2025 [8].

Cerebral infarction (CI), also known as brain infarction and ischemic stroke, is a disease of local ischemic necrosis or malacia caused by ischemia and hypoxia in brain tissues in the case of insufficient blood supply to the brain, which generally includes cerebral thrombosis, lacunar infarction, *etc*. [9]. According to researches, CI is the main type of stroke, accounting for about 80% of total cases. In addition, CI

is a disease with sudden onset, critical condition and rapid progression. It can attack people of all ages. CI patients usually have such symptoms as encephaledema, increased intracranial pressure, coma and even cerebral hernia due to wide-area infarction of internal carotid artery or middle cerebral artery. Delayed treatment often leads to poor prognosis [10]. Hypertension is clinically found to be an independent risk factor for CI. Further mechanism analysis showed that this was because hypertension damaged the blood vessel endothelium to a certain extent and thus increased the probability of platelet aggregation. In recent years, medical staffs have been committed to seeking for some indices to predict the occurrence of CI in hypertensive patients so that the predictive intervention can be performed to improve the prognosis of hypertensive patients [11].

Homocysteine (Hcy) is an important metabolic intermediate in human body. Many studies showed that Hcy may be the independent risk factor for atherosclerosis and other cardiovascular diseases. Some other investigations have indicated that Hcy is abnormally expressed in blood samples of hypertensive patients complicated with CI. This implied that this factor may be correlated with the occurrence of CI in hypertensive patients [12, 13]. Some studies have found that inflammatory factors are also abnormally highly expressed in hypertensive patients complicated with CI. This was because ischemia and hypoxia could cause the death of brain cells and thus activate the immune system [14]. This study aimed to explore the correlation of levels of Hcy and inflammatory factors with CI in hypertensive patients so as to seek for early-warning indices of CI for hypertensive patients and thus provide a theoretical basis for the improvement of quality of life (QOL) in clinical practice. The details are shown below.

Materials and methods

General materials

A total of 122 hypertensive patients treated in our hospital were selected as the objects of the study and divided into stroke group (SG, n=51) and non-stroke group (NSG, n=71) according to whether they were diagnosed with CI. Besides, 50 healthy individuals were selected and included in control group.

Inclusion criteria: (1) SG was in a state of typical hypertension and diagnosed with CI through imaging evaluation; (2) NSG suffered from hypertension, without any symptom of CI based on detection; (3) Three groups all had complete medical records; (4) The investigation was conducted with the permission of Ethics Committee of the First People's Hospital of Wenling; (5) All individuals involved or their family members had a clear understanding of procedures, methods and principles and signed the Informed Consent Form.

Exclusion criteria: (1) Patients complicated with mental diseases; (2) Those complicated with malignant tumors; (3) Those complicated with acute or chronic systemic inflammation; (4) Those complicated with brain tumors, cerebral hemorrhage, acute infarction or other diseases that affected investigation results; (5) Those complicated with autoimmune diseases; (6) Those who took the drugs that affected the metabolism of Hcy within 1 month or so; (7) Those complicated with hematological diseases; (8) And female patients in gestation period or lactation period were excluded from the study.

Intervention methods

Collection of blood samples: 5 ml of fasting venous blood was collected from SG, NSG and CG in the early morning. A part of blood samples were centrifuged by centrifugal machine at the speed of 3000 r/min and then stored at the temperature of -80°C. The indices were detected after the collection of all samples.

Treatment of CI: After admission to hospital, SG received clinical examinations actively, including brain CT scanning, MRI examination, and detection of hepatic and renal function, coagulation function, cardiac function and ambulatory blood pressure, *etc*. Meanwhile, the patients of SG in acute stage stayed in bed as much as possible and received nutritional intervention. In addition, such drugs as mannitol and furosemide, *etc*. were used for active treatment of encephaledema. Streptokinase, urokinase, barbiturate and heparin calcium were used as early as possible for thrombolysis, cerebral protection and anticoagulation treatment.

Observation targets and evaluation criteria

Comparison of laboratory indices among the three groups: The levels of Hcy, cholesterol

Table 1. Comparison of general clinical data among the three groups ($\bar{x} \pm s$)/[n (%)]

General clinical data		SG (n=51)	NSG (n=71)	CG (n=50)	*F*	*P*
Gender	Male	30	40	28	0.434	0.872
	Female	21	31	22		
Average age (years)		51.19±3.32	51.09±3.41	51.21±3.21	0.133	0.901
Average weight (kg)		59.18±3.22	59.11±3.18	59.31±3.02	0.213	0.891
Educational level	Illiteracy	3	4	4	0.531	0.802
	Primary school	6	6	5		
	Junior high school	14	21	15		
	Senior high school or above	28	40	26		
Marital status	Married	46	61	45	0.657	0.786
	Single	5	10	5		
Family income	<1,000	7	11	5	0.887	0.651
	1,000-3,000	14	20	14		
	More than 3,000	30	40	31		

(TC), triacylglycerol (TG), low density lipoprotein cholesterol (LDL-C), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and C-reaction protein (CRP) in blood samples were detected and compared among the three groups. Thereinto, the Hcy level was detected through high performance liquid chromatography (HPLC). The kit was purchased from Shanghai Jining Industrial Co., Ltd. and used in strict accordance with instructions. The levels of TC, TG and LDL-C were detected directly through automatic biochemical analyzer (purchased from Shandong BIOBASE). The levels of TNF-α and IL-6 were detected through enzyme linked immunosorbent assay (ELISA) and the kit was purchased from Quanzhou Jiubang Biotechnology Co., Ltd. All the indices mentioned above were detected for 3 times to take the mean value as final result.

Changes of Hcy, TNF-α and National Institutes of Health Stroke Scale (NIHSS) scores before and after treatment in SG: The Hcy, TNF-α and NIHSS scores of SG were detected and evaluated before treatment and at 30, 60 and 90 d after treatment and compared between groups. Thereinto, the levels of Hcy and TNF-α were detected through above method. NIHSS was used to evaluate the neurological function. It is a common, simple and reliable scale to evaluate the neurological function of stroke patients in clinical practice, including 11 items, such as level of consciousness, staring, visual field, facioplegia, upper limb movement and lower limb movement, *etc*. NIHSS is mainly used to evaluate the degree of neurological impairment. The scores ranged from 0 to 42, with 0-1 standing for normal neurological function; 1-4 for mild stroke; 5-15 for moderate stroke; 16-20 for moderate-severe stroke; and 21-42 for severe stroke. Generally, the patients with >16 scores have a higher risk of death [15].

Statistical analysis

The data collected were put into SPSS20.0 software for statistical analysis. The measurement data were expressed as ($\bar{x} \pm s$). Student's t test was used for comparison between groups. The measurement data were expressed as [n (%)]. Chi-square test was used for comparison between groups and F test was used for comparison among groups. $P<0.05$ meant that the difference had statistical significance [16].

Results

Comparison of general clinical data among the three groups

There was no statistically significant difference in gender, age, body weight, family income, educational level, marital status, *etc*. among the three groups, which was comparable ($P>0.05$) (**Table 1**).

Comparison of Hcy, TC, TG and LDL-C among the three groups

The laboratory detection showed that the levels of Hcy, TC, TG and LDL-C in SG were significantly higher than those in NSG and CG, and those of NSG were significantly higher than those of CG,

Table 2. Comparison of Hcy, TC, TG and LDL-C among the three groups ($\bar{x} \pm s$)

Group	Number of cases	Hcy (μmol/L)	TC (mmol/L)	TG (mmol/L)	LDL-C (mmol/L)
SG	51	20.27±3.21*,#	13.28±2.11*,#	3.98±0.32*,#	4.91±0.33*,#
NSG	71	15.22±2.98*	10.27±2.03*	2.18±0.44*	3.81±0.35*
CG	50	10.28±2.11	6.08±0.31	1.76±0.21	2.71±0.21

Note: * meant $P<0.05$ in comparison with CG; and # meant $P<0.05$ in comparison with NSG.

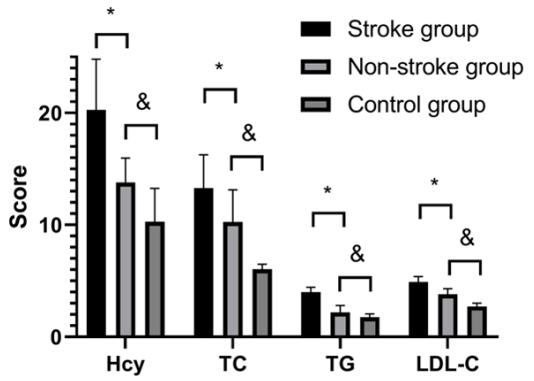

Figure 1. Comparison of Hcy, TC, TG and LDL-C among the three groups. The levels of Hcy, TC, TG and LDL-C in NSG were much higher than those in CG, showing significant difference ($P<0.05$). The levels of Hcy, TC, TG and LDL-C in SG were much higher than those in NSG, showing statistical difference ($P<0.05$). * and & referred to the statistical difference in the same index between groups.

showing significant difference between groups ($P<0.05$) (**Table 2** and **Figure 1**).

Comparison of TNF-α, CRP and IL-6 among the three groups

The laboratory detection showed that the levels of TNF-α, CRP and IL-6 in SG were significantly higher than those in NSG and CG, and those of NSG were much significantly those of CG, showing statistical difference between groups ($P<0.05$) (**Table 3** and **Figure 2**).

Changes of Hcy, TNF-α and NIHSS scores before and after treatment in SG

Based on the treatment, follow-up visit, laboratory detection and scale evaluation provided for SG, the levels of Hcy and TNF-α and NIHSS scores were reduced significantly in SG with the progress of treatment. The SG expressed higher Hcy, TNF-α and NIHSS scores before treatment than those at 30, 60 and 90 d after treatment, indicating statistical difference ($P<0.05$) (**Table 4** and **Figure 3**).

Discussion

Due to the rapid development of society in recent years, the life style and dietary structure of Chinese people have changed greatly. With the emergence of social aging and the aggravation of unhealthy living habits, the incidence of cardiovascular and cerebrovascular diseases is increasing year by year. Hypertension is a disease typically characterized by abnormal increase of systolic blood pressure or/and diastolic blood pressure. Through the examination of mercurial sphygmomanometer, hypertensive patients mostly have systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg. At present, it is not only the most common chronic disease in clinical practice, but also the main risk factor for cardiovascular and cerebrovascular diseases [17]. Clinical studies have shown that long-term hypertension can cause multiorgan dysfunction or organic injury in heart, brain, kidney, *etc*. These clinical symptoms are not obvious in the early stage. However, with the progression of hypertension, patients will have pathologic changes, such as spasm and sclerosis of arterioles, and intimal lipid deposition of main and medium-sized arteries. Above lesions can easily lead to atherosclerotic plaque or thrombogenesis and further cause multiorgan dysfunction or organic injury due to ischemia and hypoxia. Some patients even suffer from cerebral hemorrhage, heart failure, kidney failure and other lesions, threatening their life safety [18]. In the past, hypertension was thought to be a senile disease, with the elderly as high-risk group. However, recent studies have found that the onset age of hypertension tends to be younger, which seriously affects the healthy life of Chinese residents.

CI, also known as ischemic stroke, is a disease of necrosis or malacia in local brain tissues caused by ischemia and hypoxia in the case of insufficient blood supply to the brain. CI is the most common lesion in stroke, approximately

Table 3. Comparison of TNF-α, CRP and IL-6 among the three groups ($\bar{x} \pm s$)

Group	Number of cases	TNF-α (pg/mL)	CRP (mg/L)	IL-6 (pg/mL)
SG	51	32.98±3.43*,#	23.87±3.41*,#	26.37±3.22*,#
NSG	71	28.28±3.01*	19.28±2.72*	20.31±2.38*
CG	50	20.18±2.33	14.11±2.83	16.27±2.71

Note: * meant $P<0.05$ in comparison with CG; and # meant $P<0.05$ in comparison with NSG.

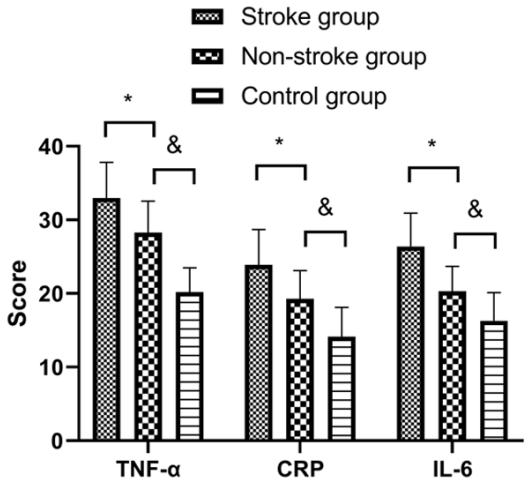

Figure 2. Comparison of TNF-α, CRP and IL-6 among the three groups. The levels of TNF-α, CRP and IL-6 in NSG were much higher than those in CG, showing significant difference ($P<0.05$). The levels of TNF-α, CRP and IL-6 in SG were much higher than those in NSG, showing significant difference ($P<0.05$). * and & referred to the statistical difference in the same index between groups.

accounting for 60%-70% of all stroke cases. The patients were mostly over 40 years old, and the prevalence in males was much higher than that in females [19]. Epidemiological investigation indicated that the incidence of CI was about 2.03% worldwide. As a common disease and frequently-occurring disease, it is one of the three leading causes of death. In some other investigations, stroke has become the leading cause of the death in China, with about 1.3 million new patients diagnosed with cerebrovascular disease each year [20]. As shown in clinical researches, CI is a disease characterized by sudden onset, critical condition, rapid progression, high fatality rate, disability rate, *etc*. Generally, patients will have such phenomena as encephaledema and increased intracranial pressure due to impaired blood supply to brain tissues. The clinical symptoms of this disease are typically sudden faint, disturbance of consciousness, lalopathy, hemiplegia, *etc*., with poor prognosis, which brings great harm and burden to the patients and their families [21]. There are many clinical studies on the correlation between hypertension and CI. According to investigations, hypertension is an independent and the most important risk factor for CI, especially manifested as abnormal elevation of blood pressure in the early morning. This phenomenon is the strongest independent predictive factor of CI. The incidence of CI increases by 44% with every increase of 10 mmHg in blood pressure in the early morning [22]. In clinical practice, many scholars have studied the correlation between hypertension and CI. In addition to the prediction of CI incidence by monitoring blood pressure, the medical staff shall emphatically study whether there are other more specific and precise indices to monitor the risk of CI in hypertensive patients.

This study analyzed the correlation of Hcy and inflammation level with the occurrence of CI among hypertensive patients by setting up different groups. The results showed that the levels of Hcy, TC, TG and LDL-C in SG and NSG were significantly higher than those in CG, suggesting that hypertension could increase the levels of Hcy, TC, TG and LDL-C to a certain extent. As mentioned above, hypertension is a high risk factor for various cardiovascular and cerebrovascular diseases. Many researches have proved that the abnormal increase of Hcy level will damage the blood vessel endothelium [23]. These results indicated that the abnormally high expression of Hcy not only caused vascular endothelial injury and hyperplasia of vascular smooth muscle, but also inhibited NO synthetase and synthesis of prostacyclin, which could increase the incidence of hypertension. TC, TG and LDL-C are common detection indices for blood lipid. Some studies showed that the patients with abnormal blood lipid were more likely to contract hypertension. In Guidelines for Management of Dyslipidemia (2011), there is an obvious correlation between TG and cardiovascular diseases. Recent studies further showed that TG was an independent risk factor of essential hypertension and LDL-C was one of the indices to detect atherosclero-

Table 4. Changes of Hcy, TNF-α and NIHSS scores before and after treatment in SG ($\bar{x} \pm s$)

Detection index	Before treatment	30 d after treatment	60 d after treatment	90 d after treatment
Hcy (μmol/L)	20.27±3.21	16.28±2.31*	14.11±1.28*	11.29±1.43*
TNF-α (pg/mL)	32.98±3.43	28.27±3.21*	23.19±3.20*	17.81±2.21*
NIHSS (scores)	15.18±2.31	11.18±1.22*	5.91±0.34*	3.18±0.34*

Note: * meant $P<0.05$ in comparison with the results before treatment.

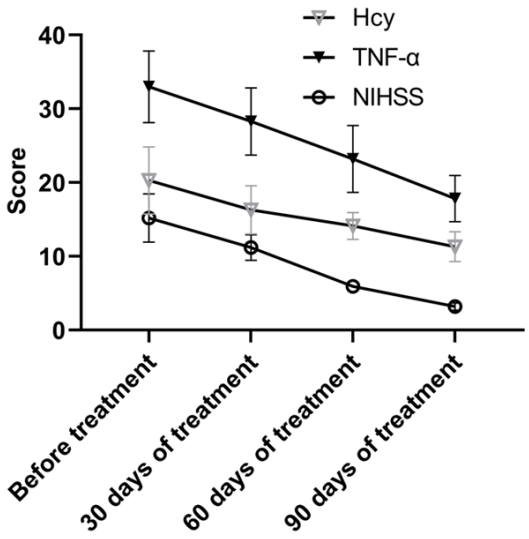

Figure 3. Changes of Hcy, TNF-α and NIHSS scores before and after treatment in SG. The Hcy level of SG were reduced significantly 30, 60 and 90 d after treatment, showing statistical difference from that before treatment ($P<0.05$). The changes of TNF-α and NIHSS scores were consistent with those of Hcy.

sis in clinical practice. Patients with high concentration of LDL-C had a higher prevalence of hypertension compared with individuals with normal LDL-C [24]. In this study, the comparison between groups showed that the levels of Hcy, TC, TG and LDL-C in SG were much higher than those in NSG, indicating that above indices could be used as predictive indices of hypertension. As mentioned above, the abnormally high expression of Hcy increased the incidence of vascular endothelial injury. Vascular endothelial injury, as one of the important lesion mechanisms for CI, can change the state of blood coagulation and cause the platelet aggregation at injury site, which will form a solid substance that protrudes from blood vessels and thus lead to thrombus. The high expressions of TC, TG, LDL-C and other indices that reflect blood lipid level can imply the state of thicker blood, which will further increase the incidence of thrombogenesis. Hence, the abnormally high expressions of Hcy, TC, TG and LDL-C can imply the increased incidence of CI in hypertensive patients.

It was also explored in this study about the correlation between inflammation level and CI among hypertensive patients. The results showed that the levels of TNF-α, IL-6 and CRP in SG and NSG were much higher than those in CG, implying that hypertensive patients were in a more active inflammatory state compared with healthy individuals. Current investigations indicated that inflammation played a crucial role in all stages of atherosclerosis and most cardiovascular risk factors had a pro-inflammatory effect. For example, hypertension played a pro-inflammatory role by mediating the expressions of various inflammatory factors, such as endothelin-1, angiotensin, *etc*. [25]. Besides, it was also indicated in animal experiments that the hormone and cellular immune function changed greatly in hypertensive animals and the disease was alleviated by injecting anti-inflammatory drugs into animals, which supported this study from the side [26]. Further comparison between groups showed that the levels of TNF-α, CRP and IL-6 in SG were much higher than those in NSG, indicating that above factors could increase the incidence of CI. Some studies indicated that the level of inflammatory factors was closely correlated with the stability of arterial plaques. The higher level of inflammatory factors indicates the poorer stability of plaques. Other studies showed that the level of inflammatory factors increased to promote human body to generate superfluous superoxides and peroxides that could stimulate blood vessel endothelium and increase the incidence of thrombogenesis. In this study, the levels of TNF-α, CRP and IL-6 in SG were much higher than those in NSG, and the Hcy, TNF-α and NIHSS scores of SG were reduced significantly after treatment, suggesting that above factors were closely correlated with the condition of HCI patients and it was possible to take Hcy and inflammatory factors as indices to predict CI in hypertensive patients.

In conclusion, the levels of Hcy and inflammatory factors were positively correlated with the

incidence of CI in hypertensive patients. The hypertensive patients with abnormally higher laboratory indices mentioned above should be treated actively to prevent CI and thus improve prognosis. As a control and prospective study, this study has following shortcomings in comparison with other similar researches. (1) The sample size was so small that the results were somewhat biased. (2) The results had no theoretical reference to a certain extent because the mechanism research was not carried out focusing on the increase of CI incidence among hypertensive patients due to abnormal increase of Hcy and inflammatory factors. In view of above shortcomings, an animal mechanism research with larger sample size and longer follow-up period shall be conducted so as to provide more precise predictive indices of CI for hypertensive patients and thus improve their prognosis and QOL effectively.

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Disclosure of conflict of interest

None.

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References

[1] Li Y, Wang L, Feng X, Zhang M, Huang Z, Deng Q, Zhou M, Astell-Burt T and Wang L. Geographical variations in hypertension prevalence, awareness, treatment and control in China: findings from a nationwide and provincially representative survey. J Hypertens 2018; 36: 178-187.

[2] Niklas AA, Flotyńska A, Zdrojewski T, Pająk A, Topór-Mądry R, Nadrowski P, Polakowska M, Kwaśniewska M, Puch-Walczak A, Bielecki W, Kozakiewicz K, Drygas W and Tykarski A. Trends in hypertension prevalence, awareness, treatment, and control among Polish adults 75 years and older during 2007-2014. Cardiol J 2018; 25: 333-344.

[3] Stoiber L, Mahfoud F, Zamani SM, Lapinskas T, Böhm M, Ewen S, Kulenthiran S, Schlaich MP, Esler MD, Hammer T, Stensæth KH, Pieske B, Dreysse S, Fleck E, Kühne T, Kelm M, Stawowy P and Kelle S. Renal sympathetic denervation restores aortic distensibility in patients with resistant hypertension: data from a multi-center trial. Clin Res Cardiol 2018; 107: 642-652.

[4] Pazoki R, Dehghan A, Evangelou E, Warren H, Gao H, Caulfield M, Elliott P and Tzoulaki I. Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events. Circulation 2018; 137: 653-661.

[5] Zhu X, Wong FKY and Wu CLH. Development and evaluation of a nurse-led hypertension management model: a randomized controlled trial. Int J Nurs Stud 2018; 77: 171-178.

[6] Bermejo J, Yotti R, García-Orta R, Sánchez-Fernández PL, Castaño M, Segovia-Cubero J, Escribano-Subías P, San Román JA, Borrás X, Alonso-Gómez A, Botas J, Crespo-Leiro MG, Velasco S, Bayés-Genís A, López A, Muñoz-Aguilera R, de Teresa E, González-Juanatey JR, Evangelista A, Mombiela T, González-Mansilla A, Elízaga J, Martín-Moreiras J, González-Santos JM, Moreno-Escobar E and Fernández-Avilés F. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial. Eur Heart J 2018; 39: 1255-1264.

[7] Yousefi M, Yaseri M, Nabizadeh R, Hooshmand E, Jalilzadeh M, Mahvi AH and Mohammadi AA. Association of hypertension, body mass index, and waist circumference with fluoride intake; water drinking in residents of fluoride endemic areas, Iran. Biol Trace Elem Res 2018; 185: 282-288.

[8] Grosso G, Stepaniak U, Micek A, Kozela M, Stefler D, Bobak M and Pajak A. Dietary polyphenol intake and risk of hypertension in the Polish arm of the HAPIEE study. Eur J Nutr 2018; 57: 1535-1544.

[9] Agyemang C, Nyaaba G, Beune E, Meeks K, Owusu-Dabo E, Addo J, Aikins AD, Mockenhaupt FP, Bahendeka S, Danquah I, Schulze MB, Galbete C, Spranger J, Agyei-Baffour P, Henneman P, Klipstein-Grobusch K, Adeyemo A, van Straalen J, Commodore-Mensah Y, Appiah LT, Smeeth L and Stronks K. Variations in hypertension awareness, treatment, and control among Ghanaian migrants living in Amsterdam, Berlin, London, and nonmigrant Ghanaians living in rural and urban Ghana - the RODAM study. J Hypertens 2018; 36: 169-177.

[10] Kramm T, Wilkens H, Fuge J, Schäfers HJ, Guth S, Wiedenroth CB, Weingard B, Huscher D, Pittrow D, Cebotari S, Hoeper MM, Mayer E and Olsson KM. Incidence and characteristics of chronic thromboembolic pulmonary hyperten-

sion in Germany. Clin Res Cardiol 2018; 107: 548-553.
[11] Souza R, Channick RN, Delcroix M, Galiè N, Ghofrani HA, Jansa P, Le Brun FO, Mehta S, Perchenet L, Pulido T, Sastry BKS, Sitbon O, Torbicki A, Rubin LJ and Simonneau G. Association between six-minute walk distance and long-term outcomes in patients with pulmonary arterial hypertension: data from the randomized SERAPHIN trial. PLoS One 2018; 13: e0193226.
[12] Li B, Yang H, Zhang W, Shi Y, Qin S, Wei Y, He Y, Yang W, Jiang S and Jin H. Fatty acid-binding protein 4 predicts gestational hypertension and preeclampsia in women with gestational diabetes mellitus. PLoS One 2018; 13: e0192347.
[13] Shuai W, Wang XX and Su H. Longitudinal change in end-digit preference in blood pressure recordings in the hypertension patients followed up in primary care clinics. Clin Exp Hypertens 2018; 40: 758-761.
[14] Petersen I, Bhana A, Folb N, Thornicroft G, Zani B, Selohilwe O, Petrus R, Mntambo N, Georgeu-Pepper D, Kathree T, Lund C, Lombard C, Bachmann M, Gaziano T, Levitt N and Fairall L. Collaborative care for the detection and management of depression among adults with hypertension in South Africa: study protocol for the PRIME-SA randomised controlled trial. Trials 2018; 19: 192.
[15] Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, Sarraj A, Kasner SE, Ansari SA, Yeatts SD, Hamilton S, Mlynash M, Heit JJ, Zaharchuk G, Kim S, Carrozzella J, Palesch YY, Demchuk AM, Bammer R, Lavori PW, Broderick JP and Lansberg MG. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018; 378: 708-718.
[16] Patel PA, Zhao X, Fonarow GC, Lytle BL, Smith EE, Xian Y, Bhatt DL, Peterson ED, Schwamm LH and Hernandez AF. Novel oral anticoagulant use among patients with atrial fibrillation hospitalized with ischemic stroke or transient ischemic attack. Circ Cardiovasc Qual Outcomes 2015; 8: 383-392.
[17] Jampathong N, Laopaiboon M, Rattanakanokchai S and Pattanittum P. Prognostic models for complete recovery in ischemic stroke: a systematic review and meta-analysis. BMC Neurol 2018; 18: 26.
[18] Bai L, Li Q, Wang J, Lavigne E, Gasparrini A, Copes R, Yagouti A, Burnett RT, Goldberg MS, Cakmak S and Chen H. Increased coronary heart disease and stroke hospitalisations from ambient temperatures in Ontario. Heart 2018; 104: 673-679.
[19] Prabhakaran S, Ruff I and Bernstein RA. Acute stroke intervention: a systematic review. JAMA 2015; 313: 1451-1462.
[20] Bechthold A, Boeing H, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, De Henauw S, Michels N, Devleesschauwer B, Schlesinger S and Schwingshackl L. Food groups and risk of coronary heart disease, stroke and heart failure: asystematic review and dose-response meta-analysis of prospective studies. Crit Rev Food Sci Nutr 2019; 59: 1071-1090.
[21] Holmes MV, Millwood IY, Kartsonaki C, Hill MR, Bennett DA, Boxall R, Guo Y, Xu X, Bian Z, Hu R, Walters RG, Chen J, Ala-Korpela M, Parish S, Clarke RJ, Peto R, Collins R, Li L and Chen Z. Lipids, lipoproteins, and metabolites and risk of myocardial infarction and stroke. J Am Coll Cardiol 2018; 71: 620-632.
[22] Nielsen PB, Skjøth F, Overvad TF, Larsen TB and Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA(2)DS(2)-VA score rather than CHA(2)DS(2)-VASc? Circulation 2018; 137: 832-840.
[23] Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, Towfighi A, Whiteley WN and Zahuranec DB. Effect of dysphagia screening strategies on clinical outcomes after stroke: a systematic review for the 2018 guidelines for the early management of patients with acute ischemic stroke. Stroke 2018; 49: e123-e128.
[24] Kim JH and Lee Y. Dementia and death after stroke in older adults during a 10-year follow-up: results from a competing risk model. J Nutr Health Aging 2018; 22: 297-301.
[25] Lou H, Dong Z, Zhang P, Shao X, Li T, Zhao C, Zhang X and Lou P. Interaction of diabetes and smoking on stroke: a population-based cross-sectional survey in China. BMJ Open 2018; 8: e017706.
[26] Xu T, Clemson L, O'Loughlin K, Lannin NA, Dean C and Koh G. Risk factors for falls in community stroke survivors: a systematic review and meta-analysis. Arch Phys Med Rehabil 2018; 99: 563-573, e565.