

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: <http://www.elsevier.com/locate/pjnns>

## Review article

## The emotional stress and risk of ischemic stroke



Dariusz Kotłęga<sup>a,\*</sup>, Monika Gołąb-Janowska<sup>a</sup>, Marta Masztalewicz<sup>a</sup>,  
Sylwester Cieciewicz<sup>b</sup>, Przemysław Nowacki<sup>a</sup>

<sup>a</sup>Department of Neurology, Pomeranian Medical University in Szczecin, Szczecin, Poland

<sup>b</sup>Department of Gynaecology and Urogynaecology, Pomeranian Medical University, Szczecin, Poland

## ARTICLE INFO

## Article history:

Received 29 December 2015

Accepted 14 March 2016

Available online 23 March 2016

## Keywords:

Risk factor

Emotional stress

Cerebral stroke

## ABSTRACT

Stroke is the second leading cause of death worldwide, and the leading cause of acquired disability in adults in most regions. There have been distinguished modifiable and non-modifiable risk factors of stroke. Among them the emotional stress was presented as a risk factor. The aim of this review was to present available data regarding the influence of acute and chronic mental stress on the risk of ischemic stroke as well as discussing the potential pathomechanisms of such relationship. There is an evident association between both acute and chronic emotional stress and risk of stroke. Several potential mechanisms are discussed to be the cause. Stress can increase the cerebrovascular disease risk by modulating sympathetic activity, affecting the blood pressure reactivity, cerebral endothelium, coagulation or heart rhythm. The emotional stress seems to be still underestimated risk factor in neurological practice and research. Further studies and analyses should be provided for better understanding of this complex, not fully known epidemiological problem.

© 2016 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

## 1. Introduction

Stroke is the second (after ischemic heart disease) leading cause of death worldwide, and the leading cause of acquired disability in adults in most regions. There have been distinguished modifiable and non-modifiable risk factors of stroke. Among them the emotional stress was presented as a risk factor. The aim of this review was to present available data regarding the influence of mental stress on the risk of ischemic stroke including the potential pathomechanisms.

The modifiable risk factors of stroke account for 88.1–90.3% of the population-attributable risks (PAR) for the association of all strokes. The most important risk factors of

ischemic stroke described as PAR are the hypertension, lack of regular physical activity, ratio of ApoB to ApoA1 apolipoproteins and waist-to-hip ratio. As presented in the INTERSTROKE multicenter study, the psychosocial factors also may increase the risk of ischemic stroke. The psychosocial stress described as a combined measure of general stress at home and in the workplace (permanent or several periods of stress vs. no or some periods of stress in the past year) was responsible for ischemic stroke risk increase (OR 1.3, 99% CI: 1.04–1.62), PAR value was calculated as 4.7%. Depression defined as feeling sad, blue, or depressed for two or more consecutive weeks during the past 12 months also modified the risk (OR 1.47, 99% CI: 1.19–1.83), PAR value was 6.8% [1].

\* Corresponding author at: Department of Neurology, Pomeranian Medical University, Unii Lubelskiej 1, 71-252 Szczecin, Poland. Tel.: +48 914253251; fax: +48 914253260.

E-mail address: [dkotlega@poczta.onet.pl](mailto:dkotlega@poczta.onet.pl) (D. Kotłęga).

<http://dx.doi.org/10.1016/j.pjnns.2016.03.006>

0028-3843/© 2016 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

## 2. Chronic emotional stress

First report of chronic psychological stress affecting the risk of ischemic stroke was revealed in a year 1990, where during 11.8 years of follow-up in 9998 men the grade of psychological stress in the last 5 years increased the risk of stroke (OR 2.0, 95% CI: 1.3–3.2, adjusted for significant risk factors only) [2]. The protocol of this report included the 5-years-lasting period of experienced stress (never or permanent) with definition of stress as a feeling of tension, anxiety and irritability. The answers were marked in a postal questionnaire by participants that might have led to not fully objective conclusions.

The association between self-reported stress frequency and intensity and risk of stroke was evaluated in a 13 years-lasting follow-up of 12,574 patients. Subjects with high stress intensity had almost a doubled risk of fatal stroke compared with subjects who were not stressed (relative risk 1.89, 95% CI: 1.11–3.21). Weekly stress was associated with an RR of 1.49 (95% CI: 1.00–2.23). There was no significant effect of stress in analyses of nonfatal strokes [3]. The definition of stress was partially different from the latter, i.e. tension, impatience, anxiety, sleeplessness. The presence of chronic stress in a 8.5-years follow-up was not related to increased risk of ischemic stroke, but a relationship was observed when highest-scoring group was compared to a lowest-scoring one (HR 1.59, 95% CI: 1.11–2.27) [4]. Another cohort study of 93,676 postmenopausal women in a follow-up to 18 years analyzed the score of stressful life events and their impact on the mood, additionally the social strain was evaluated as the measure of negative aspects of social relationships. The high social strain group was at higher risk of incident ischemic stroke when compared to low-risk group (HR 1.15, 95% CI: 1.02–1.28). On the other hand there was no association between risk of ischemic stroke and stressful life events [5]. In a follow-up of 6019 participants lasting for 16 years it has been shown that higher levels of anxiety symptoms were associated with higher risk of stroke (both ischemic and intracerebral hemorrhage). Findings suggested a dose–response relation, with every 1 SD increase in anxiety associated with a 17% increase in stroke risk when adjusting for demographic factors [6]. The investigation of only one factor such as anxiety indicates on the mental health well-being as the significant factor in the stroke pathogenesis, but should be distinguished from the stress as a general term. On the other hand anxiety may be more precisely defined and compared between researches with the use of neuropsychological tests. The high score of life events questionnaire and stressful habits were connected with higher risk of stroke in a case–control study on 150 stroke patients [7]. Even though there was relatively small sample size presented in this study, it should be noted that precise and clearly described methods were used in the research protocol such as Holmes & Rahe questionnaire of life events, recall scale of type A behavior (ERCTA), Quality of Life scale (SF12) and general health questionnaire (GHQ28).

There is an association between psychological distress and risk of death due to cardiovascular disease (ischemic heart disease and cerebrovascular disorders). In a total number of 68,652 participants, relative to those with no symptoms of psychological distress at baseline, people with psychological

distress had an increased risk of death from cerebrovascular disease (HR 1.66, 95% CI: 1.32–2.08) [8]. In a cohort study of 237,879 males the association of stress resilience in adolescence with subsequent stroke risk was investigated. Lowest stress resilience compared with the highest was associated with increased stroke risk, producing unadjusted HR of 1.54 (95% CI: 1.40–1.70). The results were consistent when stroke was subdivided into fatal, ischemic and hemorrhagic, with higher magnitude associations for fatal rather than non-fatal, and for hemorrhagic rather than ischemic stroke [9]. In a population-based study conducted on 4120 aged 65 and older participants the psychosocial distress was investigated in relation to stroke mortality and incident stroke over 6 years of follow-up. Psychosocial distress was an analytically derived composite measure of depressive symptoms, perceived stress, neuroticism, and life dissatisfaction. Adjusting for age, race, and sex, the hazard ratio (HR) for each 1 SD increase in distress was 1.47 (95% CI: 1.28–1.70) for stroke mortality and 1.18 (95% CI: 1.07–1.30) for incident stroke. Associations were reduced after adjustment for stroke risk factors and remained significant for stroke mortality (HR 1.29, 95% CI: 1.10–1.52) but not for incident stroke (HR 1.09; 95% CI: 0.98–1.21). Secondary analyses of stroke subtypes showed that distress was strongly related only to incident hemorrhagic strokes, but not ischemic strokes in fully adjusted models [10]. The variability of results in the sub-types of strokes may result from different pathogenetic background in the particular types of cerebrovascular episodes, thus we concentrate on the ischemic stroke. In the preceding year before stroke only the long-term severely threatening events were more often in 113 stroke patients compared to controls (26% vs. 13%, OR 2.3, 95% CI 1.1–4.9). Non-threatening events, events with only a short-term threat and difficulties were not increasing the risk of stroke [11].

Not only the stress assessed in a longer period, but also the neighborhood may affect the risk of stroke as shown in a study of 5789 participants. Neighborhood-level social cohesion measured by using the self-assessment protocol describing the selected aspects of neighborhood interactions. A higher score of calculated cohesion level was an independent factor reducing the stroke mortality. Each point of this calculated score was responsible for 53% reduction of stroke mortality (HR 0.47, 95% CI: 0.26–0.86). On the other hand there was no such an effect in relation to stroke incidence [12]. The socioeconomic status affects the risk of ischemic stroke by increasing the risk of incident ischemic stroke in the most disadvantaged neighborhoods among whites, but not among blacks [13]. There are also differences in stroke mortality rates depending on the level of poverty, education, population density, population mobility and race/ethnicity pattern [14]. Such observations may be connected with stress, but what is more likely – with the lifestyle, medication use and access to healthcare providers. This example indicates on a complex impact of the stress in the stroke pathogenesis and possibility of both direct and indirect impact on the risk of stroke. Supporting such a thesis it may be mentioned that the grade of socioeconomic status is associated with the major risk factors of stroke [15].

We presented different aspects of chronic stress affecting the risk of stroke. Another type of stressful factor is the workplace environment as a growing number of population

spend long time at work. As a secondary consequence it may lead to a burnout syndrome which adds to a chronic stress level in individuals. In a meta-analysis of 2023 stroke events investigating the association between a job strain and risk of ischemic stroke, the psychosocial stress at work increased the risk of ischemic stroke (HR 1.24, 95% CI: 1.05–1.47) [16]. It also should be noted that such an aspect of chronic stress has presumably huge impact on everyday level of stress. If concerned to a general level of stress, presented result might be different. Dependency between particular chronic stress aspects was examined in small number of studies.

Taking into consideration several aspects of chronic stress together, such as the workplace, general stress and stressful life events, there has been demonstrated only a tendency in increasing the risk of ischemic stroke in a recent meta-analysis (HR 1.4, 95% CI: 1.00–1.97;  $p = 0.05$ ) [17]. This result may raise some doubts as a definite conclusion, because it has some limitations. It is difficult to compare particular studies as there are rarely similar, easily comparable methodological solutions used.

### 3. Acute emotional stress

Presented results indicate on relation between chronic stress and increased risk of stroke, but there are also data regarding the acute stressful situations and incident stroke. First observations of such patients were presented in a year 1956 [18].

There is a study where 247 ischemic stroke patients were interviewed into exposition of stressful life events within one week and one month before stroke compared to such periods in the past. Patients were exposed to  $\geq 1$  life events more often during the first month preceding stroke onset than during the five control periods (OR 2.96, 95% CI: 2.19–4.00). Over the four-week period, 97 patients were exposed to  $\geq 1$  life events. Patients were exposed to  $\geq 1$  life events more often during the first week preceding stroke onset than during the three control periods (OR 2.10, 95% CI: 1.40–3.17). Such observations may lead to a conclusion that recent life events exposure is associated with an increased risk of ischemic stroke [19].

In a hospital-based observational cross-sectional study including 224 ischemic stroke patients, 11 well-established and potential trigger factors were present prior to stroke onset in 46.4% patients (analyzed in predefined hazard periods). Psychological stress within 1 month before the onset was the most common and was present in 16.5% of all stroke patients [20]. During the 2-h hazard period as much as 38% ischemic stroke patients reported potential triggers including the negative and positive emotions [21].

On the other hand in a case-control study of 37 ischemic stroke patients there was no connection between incident ischemic stroke and potentially major stressful experience within the past month [22]. In a study of 24,315 ischemic stroke and 16,088 TIA patients it was observed that number of vascular events during the birthday was higher than the expected daily number. Multivariate logistic regression showed that birthday vascular events (stroke, TIA, acute myocardial infarction) were more likely to occur in patients with a history of hypertension (OR 1.88, 95% CI: 1.09–3.24) [23].

In opposition to the chronic stress topic, in this part of paper the methods were more precisely described, but still there may be difficulties in comparing particular studies as different definitions were used. A lack of unified methods limits the statistical and practical values of presented studies. That is why we discuss potential role of stress in the risk of stroke in relation to the pathogenetic interactions.

### 4. Potential pathomechanisms

There is evident association between emotional stress and risk of stroke, but several mechanisms may be involved. Stress can either produce neurovegetative effects that predispose to psychosomatic diseases or such stress can directly relate to an increase of cerebrovascular disease risk by increasing excessive sympathetic activity. Although its role as a risk factor for stroke seems plausible, the mechanism by which psychosocial stress affects the vascular system, such as the cerebral endothelium, coagulation, or heart rhythm, has not yet been established [24]. The physiological reaction in response to stress may be presented as a multidirectional reaction including the activation of sympathetic nervous system, hypothalamic-pituitary-adrenal axis and vagal nerve withdrawal. These processes induce hemoconcentration, endothelial dysfunction and inflammatory state respectively [25].

Similarly, the exaggerated sympathetic stimulation is discussed as the cause of the fact that emotional stress can precipitate severe, reversible left ventricular dysfunction in patients without coronary disease [26]. During acute stress atherosclerotic vessels are characterized by endothelial dysfunction with decreased nitric oxide production, resulting in loss of anticoagulant and profibrinolytic properties of endothelial cells that lead to exaggerated hypercoagulability. Acute mental stress induces qualitative changes in several procoagulant molecules such as fibrinogen, factor XII:C, factor VII:C, factor VIII:C, von Willebrand factor antigen, platelet activity, thrombin-antithrombin complex, fibrin D-dimer as well as profibrinolytic tissue-type plasminogen activator. The impact of procoagulant activity is stronger than profibrinolytic resulting in hypercoagulation. The chronic emotional stress and psychiatric disorders in a similar way lead to a hypercoagulation by promoting the procoagulant molecules and reducing the fibrinolytic activity. An important factor in this process is the catecholamines release that shows multidirectional activity. Laboratory results may also be modified by the acute stress, i.e. prothrombin time and activated partial thromboplastin time. Exaggerated hypercoagulability in the response to acute mental stress may occur in the presence of modulators such as: older age, male sex, low socioeconomic status, cardiovascular disease, chronic psychosocial stress, negative affect, perceived threat and challenge [27,28]. In the healthy individuals the acute stress and subsequent increased coagulation does not have to be harmful for vessels leading to a vascular episode. The hypercoagulable state may be more important in provoking such disease in individuals with previously existing disorders. Such a pathomechanism may play a role in the atherosclerotic patients with stable coronary heart disease transformed to acute coronary syndrome [29].

Similar interaction between prothrombotic condition (inherited or acquired) and precipitating factor contribute to the development of an acute venous thromboembolism [30]. These findings are consistent with the result of a study in which noted a lower risk of a myocardial infarct triggered by an anger in patients that had been using aspirin before compared to non-users (relative risk 1.4 vs. 2.9,  $p < 0.05$ ). Aspirin users were more prone to alleviate the initial hypercoagulable state [31].

According to the mentioned observations an ischemic stroke can be provoked by an acute stress in individuals with previous traditional, in majority the vascular risk factors. A special group of stroke patients are those with the history of a cancer that constitutes approximately 7% of all ischemic stroke patients. A previous malignancy increases a risk of stroke, recurrent stroke and cardiovascular mortality. The acute stress may trigger an ischemic stroke in such patients due to the present significant hypercoagulation in the course of a cancer or its previous treatment. Such a relationship has not been studied yet [32].

Another potential pathomechanism linking the acute stress and cerebrovascular episode may be an altering of the immune system. In an experimental study of bungee jumping it has been shown that such a stressful situation significantly increases leukocyte counts, chemokine interleukin-8, proinflammatory cytokine Tumor Necrosis Factor-alpha (TNF-alpha) with unaltered induction of the anti-inflammatory cytokine Il-10 [33]. On the other hand an increased level of cortisol, an immunosuppressive hormone, is observed as a response to stress [34]. There is also a report of interactions between inflammation and coagulation in response to an acute mental stress. The D-dimer reactivity is associated with fibrinogen, Il-6 and cortisol induction to stress. Fibrin formation is related to the stress-induced activity of fibrinogen, Il-6 and activity of hypothalamo-pituitary-adrenal axis [35]. The link between inflammation measured in relation to the C-reactive protein level and response to stress is observed also in the chronic psychosocial stress as presented in a systematic review [36].

Silent cerebrovascular disease which is pathogenetically linked to a hypertension and stroke may also be of importance in this discussion. The silent cerebrovascular disease by means of the periventricular white matter hyperintensities (WMH) is commonly observed in the generally healthy adults. It was found in 83% of elderly adults (>65 years old) without previous stroke. Its role was proved to be significant in the development of atherosclerosis, dementia and stroke. The severity of WMH lesions is associated with the risk of cognitive decline and hypertension. The higher values of the blood pressure in the 24-h record and left ventricular hypertrophy are related to greater severity of WMH in the hypertensive patients. Moreover, the stress-induced reactivity of blood pressure is associated with the presence of the silent infarcts and WMH [37,38]. In a group of apparently healthy elderly adults, the values of blood pressure including the additional characteristics such as the casual, awake and sleep blood pressure, nocturnal fall and sleep variability – were associated with the enhanced presence of WMH [39]. The variability of blood pressure in response to an acute stress is reflecting the sympathetic reactivity and may exaggerate the development

of atherosclerosis, coronary heart disease, carotid intima-media complex thickening and stroke incidence. When compared high reactivity to low reactivity individuals, the risk of any stroke incidence was increased by 72% in the 11 years of follow-up period (relative risk 1.72, 95% CI: 1.17–2.540) and 87% for ischemic stroke only (relative risk 1.87, 95% CI: 1.20–2.89) [40]. The carotid intima-media complex thickness (IMT) is used as a systemic atherosclerosis marker and predicts future cardiovascular episodes. It has been noted that mean and maximum IMT correlates with the blood pressure reactivity to an acute mental stress. The same results were obtained regarding the average carotid atherosclerotic plaque [41]. The IMT and plaque severity may be connected not only with the blood pressure reactivity, but also the heart rhythm reactivity in response to an acute stress [42].

The psychological distress could also result in arterial endothelial injury. Studies show that posttraumatic stress disorder (PTSD) victims have higher circulating catecholamines and other sympathoadrenal-neuroendocrine bioactive agents implicated in arterial damage. There were atrioventricular conduction defects detected more often in the PTSD patients, while depression was associated with arrhythmias [43].

Mental stress produces significant effects on the electrophysiologic properties of the heart [44]. Atrial fibrillation is an important pathogenic factor and cause of stroke, it is of importance that the acute life stress during 30 days before the occurrence of first episode of atrial fibrillation was more often than compared to controls [45]. In a long term follow-up the high job-strain was related to increased risk for AF (HR 1.32, 95% CI: 1.003–1.75) [46].

Taking into consideration these observations, both direct and indirect links may be responsible for modulating the risk of ischemic stroke in case of the acute stress. Discussing the atrial fibrillation effect, it may lead to stroke and acute stress may only be the trigger factor as mentioned above or part of the multidirectional effect of several risk factors. It would be of interest to investigate particular factors independently. It is not clear whether there is the separate impact of particular aspects of mental stress on the risk of stroke. This statement concerns both chronic and acute stress. On the other hand it is very likely that complex interaction plays role in the stroke pathogenesis between most of the presented neuropsychological aspects. Presumably, common background such as personality, childhood and attitude to chronic stress also predispose to the harmful effect of an acute stress.

---

## 5. Conclusions

The emotional stress, both acute and chronic are not often discussed risk factors of ischemic stroke. In this review we described the present state of knowledge within this field and potential pathogenetic background. Both acute and chronic stress is significant and multidirectionally connected with the risk of ischemic stroke. This risk factor seems to be still underestimated in neurological practice and research. On the other hand there is also a possibility that stress is overestimated risk factor of stroke as there have not been demonstrated in a satisfactory extent consistent, clear tools for precise, objective measurements and validated methods.

Further studies and analyses should be provided for better understanding of this complex, not fully known epidemiological problem. Unified examination methods and definitions are suggested for the future studies.

### Conflict of interest

None declared.

### Acknowledgement and financial support

None declared.

### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

### REFERENCES

- [1] O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al., INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;376:112–23. [http://dx.doi.org/10.1016/S0140-6736\(10\)60834-3](http://dx.doi.org/10.1016/S0140-6736(10)60834-3)
- [2] Harmsen P, Rosengren A, Tsipogianni A, Wilhelmsen L. Risk factors for stroke in middle-aged men in Göteborg, Sweden. *Stroke* 1990;21:223–9. <http://dx.doi.org/10.1161/01.STR.21.2.223>
- [3] Truelsen T, Nielsen N, Boysen G, Grønbaek M. Self-reported stress and risk of stroke: the Copenhagen City Heart Study. *Stroke* 2003;34:856–62. <http://dx.doi.org/10.1161/01.STR.0000062345.80774.40>
- [4] Everson-Rose SA, Roetker NS, Lutsey PL, Kershaw KN, Longstreth Jr WT, Sacco RL, et al. Chronic stress, depressive symptoms, anger, hostility, and risk of stroke and transient ischemic attack in the multi-ethnic study of atherosclerosis. *Stroke* 2014;45:2318–23. <http://dx.doi.org/10.1161/STROKEAHA.114.004815>
- [5] Torén K, Schiöler L, Giang WK, Novak M, Söderberg M, Rosengren A. Occupational and environmental medicine: a longitudinal general population-based study of job strain and risk for coronary heart disease and stroke in Swedish men. *BMJ Open* 2014;4:e004355. <http://dx.doi.org/10.1136/bmjopen-2013-004355>
- [6] Lambiase MJ, Kubzansky LD, Thurston RC. Prospective study of anxiety and incident stroke. *Stroke* 2014;45:438–43. <http://dx.doi.org/10.1161/STROKEAHA.113.003741>
- [7] Egido JA, Castillo O, Roig B, Sanz I, Herrero MR, Garay MT, et al. Is psycho-physical stress a risk factor for stroke? A case-control study. *J Neurol Neurosurg Psychiatry* 2012;83:1104–11. <http://dx.doi.org/10.1136/jnnp-2012-302420>
- [8] Hamer M, Kivimäki M, Stamatakis E, Batty GD. Psychological distress as a risk factor for death from cerebrovascular disease. *CMAJ* 2012;184:13. <http://dx.doi.org/10.1503/cmaj.111719>
- [9] Bergh C, Udumyan R, Fall K, Nilsagård Y, Appelros P, Montgomery D. Stress resilience in male adolescents and subsequent stroke risk: cohort study. *J Neurol Neurosurg Psychiatry* 2014;85:1331–6. <http://dx.doi.org/10.1136/jnnp-2013-307485>
- [10] Henderson KM, Clark CJ, Lewis TT, Aggarwal NT, Beck T, Guo H, et al. Psychosocial distress and stroke risk in older adults. *Stroke* 2013;44:367–72. <http://dx.doi.org/10.1161/STROKEAHA.112.679159>
- [11] House A, Dennis M, Mogridge L, Hawton K, Warlow C. Life events and difficulties preceding stroke. *J Neurol Neurosurg Psychiatry* 1990;53:1024–8. <http://dx.doi.org/10.1136/jnnp.53.12.1024>
- [12] Clark CJ, Guo H, Lunos S, Aggarwal NT, Beck T, Evans DA, et al. Neighborhood cohesion is associated with reduced risk of stroke mortality. *Stroke* 2011;42:1212–7. <http://dx.doi.org/10.1161/STROKEAHA.110.609164>
- [13] Brown AF, Liang LJ, Vassar SD, Stein-Merkin S, Longstreth Jr WT, Ovbiagele B, et al. Neighborhood disadvantage and ischemic stroke: the Cardiovascular Health Study (CHS). *Stroke* 2011;42:3363–8. <http://dx.doi.org/10.1161/STROKEAHA.111.622134>
- [14] Balamurugan A, Delongchamp R, Bates JH, Mehta JL. The neighborhood where you live is a risk factor for stroke. *Circulation* 2013;128:668–73. <http://dx.doi.org/10.1161/CIRCOUTCOMES.113.000265>
- [15] Pipatvanichgul B, Hanchaiphiboolkul S, Puthkhao P, Tantirittisak T, Towanabut S. Association between socioeconomic status and major risk factors of stroke: Thai Epidemiologic Stroke (TES) study. *J Med Assoc Thai* 2015;98:739–47.
- [16] Fransson EI, Nyberg ST, Heikkilä K, Alfreðsson L, Björner JB, Borritz M, et al. Job strain and the risk of stroke: an individual-participant data meta-analysis. *Stroke* 2015;46:557–9. <http://dx.doi.org/10.1161/STROKEAHA.114.008019>
- [17] Booth J, Connelly L, Lawrence M, Chalmers C, Joice S, Becker C, et al. Evidence of perceived psychosocial stress as a risk factor for stroke in adults: a meta-analysis. *BMC Neurol* 2015;15:233. <http://dx.doi.org/10.1186/s12883-015-0456-4>
- [18] Ecker A. Emotional stress before strokes: a preliminary report of 20 cases. *Ann Intern Med* 1954;40:49–56. <http://dx.doi.org/10.7326/0003-4819-40-1-49>
- [19] Guiraud V, Touzé E, Rouillon F, Godefroy O, Mas JL. Stressful life events as triggers of ischemic stroke: a case-crossover study. *Int J Stroke* 2008;300–7. <http://dx.doi.org/10.1111/j.1747-4949.2012.00810.x>
- [20] Sharma A, Prasad K, Padma MV, Tripathi M, Bhatia R, Singh MB, et al. Prevalence of triggering factors in acute stroke: hospital-based observational cross-sectional study. *J Stroke Cerebrovasc Dis* 2015;24:337–47. <http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.08.033>
- [21] Koton S, Tanne D, Bornstein NM, Green MS. Triggering risk factors for ischemic stroke: a case-crossover study. *Neurology* 2004;63:2006–10.
- [22] Macko RF, Ameriso SF, Barndt R, Clough W, Weiner JM, Fisher M. Roles of preceding infection/inflammation and recent psychological stress. *Stroke* 1996;27:1999–2004. <http://dx.doi.org/10.1161/01.STR.27.11.1999>
- [23] Saposnik G, Baibergenova A, Dang J, Hachinski V. Does a birthday predispose to vascular events? *Neurology* 2006;67:300–4.
- [24] Brainin M, Dachenhausen A. Psychosocial distress, an underinvestigated risk factor for stroke. *Stroke* 2013;44:305–6. <http://dx.doi.org/10.1161/STROKEAHA.112.680736>
- [25] Austin AW, Wissmann T, von Kanel R. Stress and hemostasis: an update. *Semin Thromb Hemost* 2013;39:902–12.
- [26] Wittstein IS, Thiemann DR, Lima JAC, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features

- of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;352:539-48. <http://dx.doi.org/10.1056/NEJMoa043046>
- [27] von Känel R. Acute mental stress and hemostasis: when physiology becomes vascular harm. *Thromb Res* 2015;135 (Suppl. 1):S52-5. [http://dx.doi.org/10.1016/S0049-3848\(15\)50444-1](http://dx.doi.org/10.1016/S0049-3848(15)50444-1)
- [28] von Känel R, Mills PJ, Fainman C, Dimsdale JE. Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease? *Psychosom Med* 2001;63:531-44.
- [29] von Känel R. Acute mental stress and hemostasis: when physiology becomes vascular harm. *Thromb Res* 2015;135 (Suppl. 1):S52-5.
- [30] Lippi G, Franchini M, Favaloro EJ. Unsuspected triggers of venous thromboembolism – trivial or not so trivial? *Semin Thromb Hemost* 2009;35:597-604. <http://dx.doi.org/10.1055/s-0029-1242713>
- [31] Mittleman MA, Maclure M, Sherwood JB, Mulry RP, Tofler GH, Jacobs SC, et al. Triggering of acute myocardial infarction onset by episodes of anger. Determinants of myocardial infarction onset study investigators. *Circulation* 1995;92:1720-5.
- [32] Lau KK, Wong YK, Teo KC, Chang RS, Hon SF, Chan KH, et al. Stroke patients with a past history of cancer are at increased risk of recurrent stroke and cardiovascular mortality. *PLoS ONE* 2014;9(2):e88283. <http://dx.doi.org/10.1371/journal.pone.0088283>
- [33] van Westerloo DJ, Choi G, Löwenberg EC, Truijien J, de Vos AF, Endert E, et al. Acute stress elicited by bungee jumping suppresses human innate immunity. *Mol Med* 2011;17:180-8. <http://dx.doi.org/10.2119/molmed.2010.00204>
- [34] Alvarez SM, Katsamanis Karavidas M, Coyle SM, Lu SE, Macor M, Oikawa LO, et al. Low-dose steroid alters in vivo endotoxin-induced systemic inflammation but does not influence autonomic dysfunction. *J Endotoxin Res* 2007;13:358-68.
- [35] von Känel R, Kudielka BM, Hanebuth D, Preckel D, Fischer JE. Different contribution of interleukin-6 and cortisol activity to total plasma fibrin concentration and to acute mental stress-induced fibrin formation. *Clin Sci (Lond)* 2005;109:61-7.
- [36] Johnson TV, Abbasi A, Master VA. Systematic review of the evidence of a relationship between chronic psychosocial stress and C-reactive protein. *Mol Diagn Ther* 2013;17:147-64. <http://dx.doi.org/10.1007/s40291-013-0026-7>
- [37] Waldstein SR, Siegel EL, Lefkowitz D, Maier KJ, Brown JR, Obuchowski AM, et al. Stress-induced blood pressure reactivity and silent cerebrovascular disease. *Stroke* 2004;35:1294-8.
- [38] Shimada K, Kawamoto A, Matsubayashi K, Ozawa T. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. *Hypertension* 1990;16:692-9.
- [39] Goldstein IB, Bartzokis G, Hance DB, Shapiro D. Relationship between blood pressure and subcortical lesions in healthy elderly people. *Stroke* 1998;29:765-72.
- [40] Everson SA, Lynch JW, Kaplan GA, Lakka TA, Sivenius J, Salonen J. Stress-induced blood pressure reactivity and incident stroke in middle-aged men. *Stroke* 2001;32:1263-70.
- [41] Kamarck TW, Everson SA, Kaplan GA, Manuck SB, Jennings JR, Salonen JT. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men. Findings from the Kuopio Ischemic Heart Disease Study. *Circulation* 1997;96:3842-8.
- [42] Matthews KA, Owens JF, Kuller LH, Sutton-Tyrrell K, Lassila HC, Wolkson SK. Stress-induced pulse pressure change predicts women's carotid atherosclerosis. *Stroke* 1998;29:1525-30.
- [43] Boscarino JA, Chang J. Electrocardiogram abnormalities among men with stress-related psychiatric disorders: implications for coronary heart disease and clinical research. *Ann Behav Med* 1999;21:227-34.
- [44] Insulander P, Juhlin-Dannfelt A, Freyschuss U, Vallin H. Electrophysiologic effects of mental stress in healthy subjects: a comparison with epinephrine infusion. *J Electrocardiol* 2003;36:301-9.
- [45] Mattioli AV, Bonatti S, Zennaro M, Mattioli G. The relationship between personality, socio-economic factors, acute life stress and the development, spontaneous conversion and recurrences of acute lone atrial fibrillation. *Europace* 2005;7:211-20. <http://dx.doi.org/10.1016/j.eupc.2004.02.006>
- [46] Torén K, Schiöler L, Söderberg M, Giang KW, Rosengren A. The association between job strain and atrial fibrillation in Swedish men. *Occup Environ Med* 2015;72:177-80. <http://dx.doi.org/10.1136/oemed-2014-102256>