RISK FACTORS FOR ISCHAEMIC STROKE: CORRELATON OF GENDER AND AGE WITH STROKE SEVERITY AND PATIENT OUTCOME

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Abstract

The risk of stroke exists regardless of gender, age, co-morbidities and lifestyle. Yet, research points out to significant differences concerning the severity of stroke and its functional outcome, correlated to gender, age as well as co-morbidities.

The aim of our study is to analyse the stroke-related risk factors, as well as to create a correlation with gender and age respecting stroke severity and patient outcome.

We conducted a retrospective analysis of 157 patients hospitalized at the Department for Urgent Neurology, at the University Clinic for Neurology in Skopje, N. Macedonia, during the period of October 2019- October2020. All of the included patients were diagnosed with ischemic stroke, confirmed by a computed tomography (CT scan) of the brain. Patient's risk factors (hypertension, diabetes, atrial fibrillation, etc.) were analyzed in relation to gender (men and women) and age (over and under the age of 50).

A comparison of stroke severity, assessed by the National Institutes of Health Stroke Scale (NIHSS) score was made, whereas the functional outcome was measured by the Modified Rankin Scale Score (mRS). All parameters were evaluated both on admission and upon discharge.

Women over 50 years of age were more likely to develop severe stroke - 43.3% (29), whereas no symptoms of severe stroke were observed in the male group of patients under 50 years of age. Moderate stroke symptoms were noticed in the majority of female and male patients under and over the age of 50 – 29.85%(20), 46.05%(35), 50%(4), in 66.7%(4) of the examined subjects, respectively.

The calculated difference of neurological deficit severity between female patients under the age of 50, female patients over 50 , male patients under 50, and male patients over the age of 50, was statistically insignificant (p =0.32). Similarly, upon discharge, the preponderance of the patients from the four groups resulted with moderate neurological deficit – 47.4%(18) female patients over 50 , 46.3%(19) male patients over 50, and 66.7%(4) female patients under 50 years of age.

Keywords: ischemic stroke, risk factors, gender, age.

Introduction

It is well known that certain risk factors exist as predictors of stroke. About a dozen of risk factors are observed and analyzed among the general populations of different age groups, genders and ethnical backgrounds. The major risk factors for stroke are the following: hypertension, smoking, dyslipidemia, unhealthy diet, physical inactivity, obesity, diabetes mellitus, heart diseases, and excessive alcohol intake in addition to other psychosocial factors [1-3].

Yet, there are certain differences regarding their representation by age and gender. According to the American Stroke Association-ASA, in the USA one in five females has a stroke, and around 55,000 more females get a stroke compared to males on a yearly level [4]. Several studies have shown that the risk factors and etiology differ between younger and older patients [5].

In such manner, migraine is frequently reported among young adults, while traditional risk factors for developing stroke, such as hypertension and dyslipidemia, are usually less present. Atherosclerosis of large arteries on the other hand, is rare, while cervical artery dissection is a common cause of cerebral stroke among young adults. Cardio-embolic stroke is in most cases caused by cardiac conditions with low to unknown embolic risk, such as patent foramen ovale and atrial septal aneurysm.

Aim

The aim of our study is to analyze the risk factors for stroke and correlate them with gender (male vs. female population) and age (under and over 50 years of age), regarding the stroke severity and the patient outcome.

Material and methods

We made a retrospective analysis of 157 patients hospitalized in a 1year period 01.10.2019-01.10.2020. They were admitted at the University Clinic of Neurology in Skopje, N. Macedonia - department of Urgent Neurology and were diagnosed with acute ischemic stroke confirmed by CT scan. Inclusion criteria were patients in all age groups with signs of acute cerebral infarction on CT scan, with the following preexisting comorbidities: hypertension (HTA), atrial fibrillation (AF), cardiomyopathy (CMP), diabetes mellitus (DM), hyperlipidemia (HLP), prior stroke or transientischemic attack (TIA). In the analysis we included other parameters such as neurologic deficit quantified by NIHSS score in 2 time periods: on admission (or in the first 24 hours) and on discharge (except for patients with lethal outcome).

Depending on the NIHSS score we divided stroke patients in 5 categories: no signs of stroke (0 points), minor stroke (1-4 points), moderate stroke (5-15 points), moderate to severe stroke (16-20 points) and severe stroke (21-42 points).

We also included level of consciousness in stroke patients quantified by Glasgow Coma Scale (GSC) score, calculated in 2 time periods: on admission and on discharge (except for patients with lethal outcome), and based on this score we divided the patients according to the level of consciousness and brain injury in 3 groups: mild injury (15-13 points), moderate injury (12-9points) and severe injury (8-3 points).

Statistical analysis

The statistical analysis of patients data was provided by the statistical programe SPSS 23,0. Shapiro Wilk's test was used to test the normality of data distribution.Categorical (atributive) variables are shown with absolute and relative numbers. Numerical (quantitive) variables are shown with mean and standard deviation.

For comparison of the scores on admission and discharge, we used "Student t-test, for dependent samples" and "Wilcoxon matcher pairs test", and for comparing scores of patients with or without risk factors we used Student t-test for independent samples.Spearman's rank correlation coefficient was used to correlate number of risk factors with both scales.Statistical significance was defined at level $p < 0.05$. Data are displayed in tables and graphics.

Results

Out of 157 stroke patients who participated in our study, 67 (42.7%) were female over the age of 50, 76 (48.4%) were male over the age of 50, 8 (5.1%) were female patients under the age of 50, and 6 (3.8%) of them were male patients under the age of 50.

According to the NIHSS score on admission, stroke symptoms were noticed in only one patient over the age of 50 out of all female and male patients under and over the age of 50, 7.5% (5) of female patients over 50 years of age, 5.3 %(4) of male patients over 50, and 1 male patient under 50 years of age

presented with mild symptoms of stroke. (table 1). Women over 50 years of age were most frequently affected by severe stroke - 43.3%(29), in contrast, no symptoms of severe stroke were noticed in theale group of patients under the age of 50. Most of women and men over and under the age of 50 experienced moderate stroke symptoms - 29.85% (20), 46.05% (35), 50% (4) and 66.7% (4) patients, respectively. The tested difference of the severity of neurological deficit among female patients under 50, female patients over 50, male patients under 50, and male patients over 50 years of age was statistically insignificant (p =0.32). In total, 88 (56%) patients were discharged from the hospital, whereas 69 (44%) of them had fatal outcome.

Similarly, on discharge, the difference between these 4 groups regarding the neurological deficit severity was insignificant (p=0.22). Among the five patients without stroke symptoms, 4 were over 50, of whom two were male, two female and one of them was a male patient under the age of 50. Severe neurological deficit on discharge presented 4 patients over 50 , 3 female and 1 male correspondingly.

Table 1. Number of patients distributed in five stroke severity categories according to NIHSS score and divided by age and gender

		Study groups				p-level
	n	female >50 n (%)	male >50 n (%)	female <50 n (%)	male <50 n (%)	
NIHSS on admission						
No stroke symptoms n (%)	1	0	1 (1.32)	0	0	Exact p=0.32 ns
Mild n (%)	10	5 (7.46)	4(5.26)	0	1 (16.67)	
Moderate n (%)	63	20 (29.85)	35 (46.05)	4 (50)	4 (66.67)	
Moderate to severe n (%)	25	13 (19.4)	10 (13.16)	1 (12.5)	1 (16.67)	
Severe n (%)	58	29 (43.28)	26 (34.21)	3 (37.5)	0	
NIHSS on discharge						
No stroke symptoms n (%)	5	2 (5.26)	2 (4.88)	0	1 (33.33)	
Mild n (%)	29	11 (28.95)	16 (39.02)	0	2 (66.67)	
Moderate n (%)	41	18 (47.37)	19 (46.34)	4 (66.67)	0	
Moderate to severe n (%)	9	4 (10.53)	3 (7.32)	2 (33.33)	0	
Severe n (%)	4	3 (7.89)	1 (2.44)	0	0	

The mean NIHSS score on admission was higher for the female group of patients over 50 (18.69 ± 9.5), and lower for the male group of patients under the age of 50 (10.33 ± 6.6) (table 2). Male patients over 50 and female patients under 50, had a similar mean NIHSS score on admission (17.64±9.9 and 17.87±8.2, respectively).

On discharge, female patients under and over the age of 50 had a higher mean score compared to men patients of the same age (11.50 ± 5.2, 9.0 ± 6.5, 7.24 ± 5.8, and 2.0 ± 1.0, respectively).

No statistically significant difference was found in the average score of the NIHSS scale, between female and male patients over and under the age of 50, both on admission and discharge (p>0.05).

Table 2. A comparison of female and male patients over and under the age of 50 regarding the mean NIHSS score on admission and discharge

	NIHSS			p-level
	n	mean±SD	min - max	
Admission				
female >50 y.o.	67	18.69 ± 9.5	2 – 35	F=1.41
male >50 y.o.	76	17.64 ± 9.9	0 – 35	p=0.24 ns
female <50 y.o.	8	17.87 ± 8.2	8 – 33	
male <50 y.o.	6	10.33 ± 6.6	2 – 20	
Discharge				
female >50 y.o.	38	9.0 ± 4.5	0 – 24	F=2.21
male >50 y.o.	41	7.24 ± 3.8	0 – 28	p=0.09 ns
female <50 y.o.	6	11.50 ± 4.2	6 – 18	
male <50 y.o.	3	2.0 ± 1.0	0 – 4	

F (Analysis of Variance)

A comparison of female and male patients over and under the age of 50 regarding the frequency of certain risk factors was made (HTA, arrhythmia, CMP, DM type2, recurrent stroke and HLP) (table 3).

According to the obtained results, no significant difference was established in the four groups concerning the frequency of cardiac arrhythmia (p=0.39), CMP (p=0.79), and recurrent stroke (p=0.61).

For p=0.009, a statistically significant difference was confirmed in the frequency of high blood pressure based on stroke patient's gender and age (Figure 1).

Intergroup comparisons showed that female patients under the age of 50 suffered from high blood pressure significantly more often than female and male patients over the age of 50 – 62.5%(5) vs 11.9%(8), p=0.002; 62.5% (5) vs 23.7 (18), p=0.019.

At the level of statistical significance, the difference in patient distribution with and without diabetes mellitus type 2 among the 4 analyzed groups was tested. (p=0.057).

All female patients under the age of 50 had type 2 diabetes, as well as 68.7% (46) female patients over the age of 50 , 71.05%(54) male patients over 50, and 33.3%(2) male patients under the age of 50.

Hyperlipidaemia (HLP) was present in 16.4%(11) of female patients over the age of 50, 3.95%(3) of male patients over the age of 50 and in one patient from the male group of patients under the age of 50 (Figure 2). A statistically significant difference was confirmed between patients from the 4 analyzed groups regarding the frequency of HLP (p=0.045), and this variation was due to a significant difference between female and male patients over the age of 50 (p=0.012).

Table 3. A comparison of female and male patients over and under the age of 50 regarding the frequency of certain risk factors

|			Gender code				p-level
			female >50 y.o. n (%)	male >50 y.o. n (%)	female <50 y.o. n (%)	male >50 y.o. n (%)	
HTA	yes	n=32	8 (11.94)	18 (23.68)	5 (62.5)	1 (16.67)	Exact
	no	n=125	59 (88.06)	58 (76.32)	3 (37.5)	5 (83.33)	p=0.009 sig 1vs 3 p=0.002 2 vs 3 p=0.019
Aarrhythmia	no	n=131	57 (85.07)	60 (78.95)	8 (100)	6 (100)	Exact
	yes	n=26	10 (14.93)	16 (21.05)	0	0	p=0.39 ns
CMP	no	n=135	59 (88.06)	63 (82.89)	7 (87.5)	6 (100)	Exact
	yes	n=22	8 (11.94)	13 (17.11)	1 (12.5)	0	p=0.79 ns
DM2	no	n=110	46 (68.66)	54 (71.05)	8 (100)	2 (33.33)	Exact
	да	n=47	21 (31.34)	22 (28.95)	0	4 (66.67)	p=0.057 ns
Recurrent stroke	no	n=120	50 (74.63)	57 (75)	7 (87.5)	6 (100)	Exact
	yes	n=37	17 (25.37)	19 (25)	1 (12.5)	0	p=0.61 ns
HLP	no	n=142	56 (83.58)	73 (96.05)	8 (100)	5 (83.33)	Exact
	yes	n=15	11 (16.42)	3 (3.95)	0	1 (16.67)	p=0.045 sig 1vs2 p=0.012
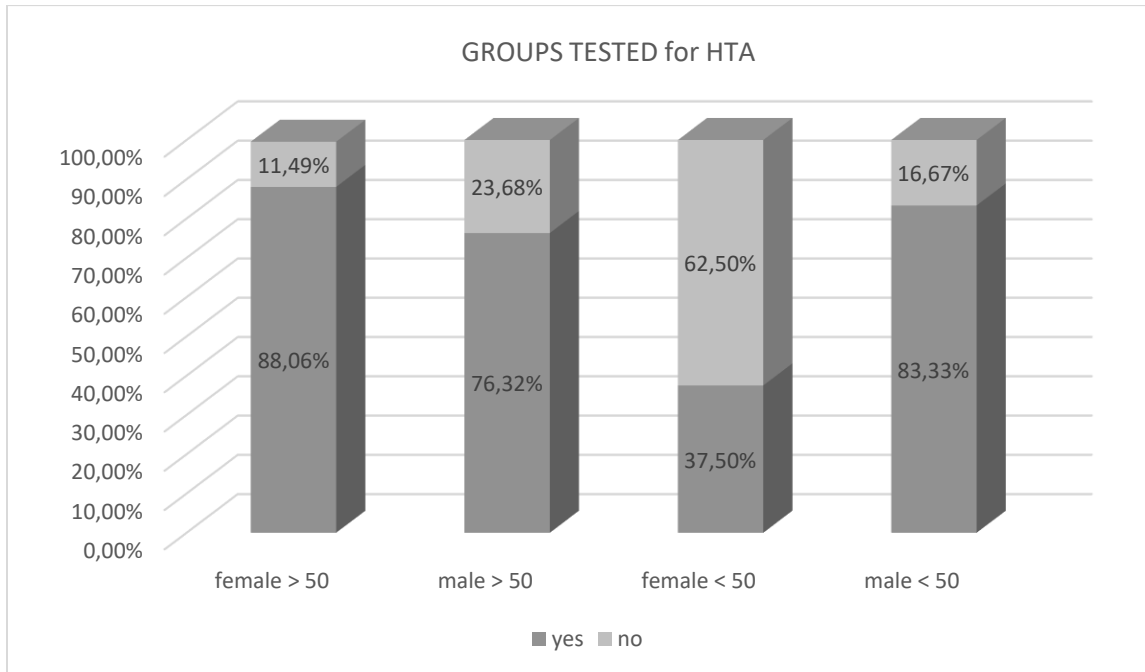
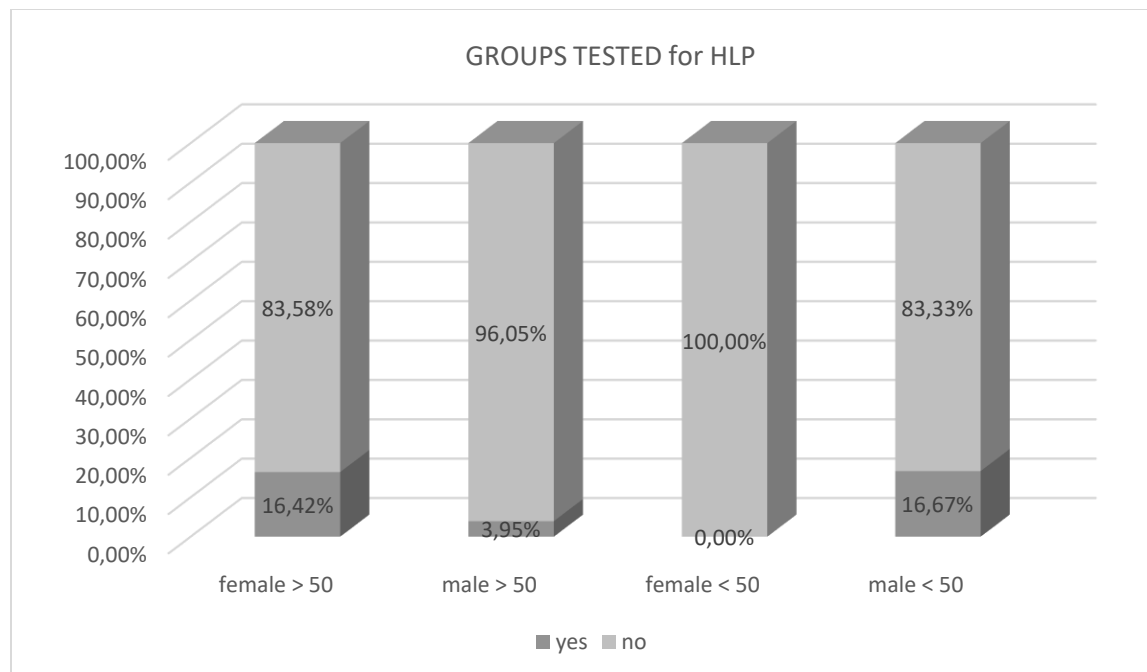**Figure 1.** Frequency of high blood pressure based on stroke patient's gender and age

Figure 2. Frequency of hyperlipidemia based on stroke patient's gender and age

Discussion

In our group of subjects, no statistically significant difference was found regarding the severity of the neurological deficit between female and male patients over and under the age of 50, both upon admission and discharge (p=0.32 and p=0.22). Despite the absence of a statistically significant difference regarding the average NIHSS score among the 4 groups of subjects (p>0.05), it should be emphasized that female patients both under and over 50 had a higher average NIHSS score as opposed to men at these ages (11.50 $\pm$ 5.2, 9.0 $\pm$ 6.5, 7.24 $\pm$ 5.8 and 2.0 $\pm$ 1.0, respectively).

Regarding the representation of risk factors, the 4 groups did not differ significantly in the frequency of cardiac arrhythmia (p=0.39), CMP (p=0.79), and recurrent stroke (p=0.61). But for p=0.009, a statistically significant difference was confirmed in the frequency of hypertension based on the gender and age of stroke patients. Intergroup comparisons showed that female patients under 50 tend to suffer from hypertension significantly more often than female and male patients over 50 – 62.5%(5) vs 11.9%(8), p=0.002; 62.5% (5) vs 23.7 (18), p=0.019.

All female patients under the age of 50 had type 2 diabetes, as did 68.7% (46) of female patients over 50, 71.05% (54) of male patients over 50, and 33.3% (2) of male patients under 50 years old.

Hyperlipidemia was present in 16.4%(11) of female patients over 50 years of age, 3.95%(3) of male patients over 50 years of age and in one participant from the male group of patients under 50 years old. A statistically significant difference was confirmed between patients from the 4 analyzed groups regarding the frequency of HLP (p=0.045), and this difference was due to a significant difference between female and male participants older than 50 years (p=0.012).

Data in the literature suggest that there are gender differences in health and mortality [6]. Women have 2 X chromosomes, so they have the possibility to compensate for a mutation, contrary to men. Also, female hormones may provide protection against some conditions. Their responses to oxidative stress and maintenance of homeostasis are different compared to men.

In the past 2 decades, many countries have conducted national-level surveys of their middle-aged and older populations that have included data on multiple dimensions of morbidity for large samples of both sexes.

Some epidemiological studies such as that of the European Multicentre Multinational Hospital-Based Registry, done on about 4,500 patients, as well as data from a systematic review of gender differences in stroke epidemiology, found that women were significantly older compared to men at the onset of stroke, with more stroke events reported in women > 80 years old [7].

A total of 1272 stroke patients were included in their analysis: 1152 ischemic and 120 hemorrhagic strokes, 567 women and 705 men. Compared to men, women were significantly older (mean age 75.2 SD 13.7 vs. 71.5 SD 12.5 years, P < 0.001), with more severe strokes, as assessed by the NIHSS score (P < 0.001). Female gender was associated with a worse functional prognosis as measured by the modified Rankin Scale (mRS) score (mRS ≥ 3), as well as with in-hospital mortality, without statistical significance. Analysis of the distribution of risk factors between sexes showed a prevalence of atrial fibrillation in women (29% vs. 21%, P = 0.003).

In this studied population, women appeared to have a more severe stroke at the beginning compared to men, as measured by the NIHSS score. The authors state that available data from the literature concerning differences in stroke severity between men and women is inconsistent [7].

It is reported that women with stroke have different symptoms compared to men. Particularly, it is reported that women tend to have aphasia, visual field disorders, and dysphagia more often than men; while no differences were reported in either motor or sensory deficits. Furthermore, stroke in women is more often associated with anterior circulation ischemia, while men are more likely to have cerebellar and brainstem symptoms and a higher incidence of posterior circulation syndromes compared to women. Concerning the state of consciousness, data indicate that the impaired level of consciousness in women occurs more often than in men, which may contribute to the greater severity of stroke in women.

The authors also present data from studies that indicate that women have less favorable outcomes, as well as more physical impairment and limitations in daily activities as measured by the Barthel Index, compared to men.

Data show a higher prevalence of AF in women compared to men, and this is probably due to their older age at the time of stroke onset, thus increasing the risk for cardio-embolic stroke in women.

Women with AF are less treated with anticoagulant therapy for primary prevention than men, and their participation in randomized clinical trials is fewer, which leads to increased risk of thromboembolic complications from AF as opposed to men.

Taking in consideration that cardio-embolic stroke is more severe compared to other stroke subtypes, the higher prevalence of AF may explain the increased severity of stroke in women.
In conclusion, this study, similar to other studies, suggests that gender differences in patients with stroke actually exist, and that women develop severe stroke at a later age, having this way a worse functional outcome in comparison to men [7].

The Bergen Stroke Study is an analysis of 100 patients (8.2%) <50 years old, with men participants predominating (72% vs. 55.8%, P = .002) [8].

Young stroke patients were more likely to be current smokers (44.1% vs. 23.6%, P < .001). Common causes of stroke in youth were cervical artery dissection (18% vs. 0.6%, P<.001) and cardiac embolism due to disorders other than atrial arrhythmias (18% vs. 5.5%, P<.001). In the elderly, atrial fibrillation and flutter predominated (29.1% vs. 5%, P < .001).

Stroke severity and location did not differ. They concluded that stroke is more frequent in men, smoking was more common among the young participants, cervical artery dissection and non-arrhythmic heart disorders were common causes in younger patients, while traditional risk factors dominated in the elderly. Stroke severity was similar, but elderly patients were more exposed to infectious complications. The authors concluded that there are important differences between young and elderly patients in terms of risk factors, etiology and gender distribution.

However, stroke severity on admission as well as the short-term outcome were similar in young and old patients.

The INSTRUCT *Meta - Analysis* of *Individual Participant Data* found that women with ischemic stroke faced a 35% higher risk of major stroke than men, and that much of this difference was explained by pre-stroke factors, including : older age of women, presence of functional limitations before stroke and atrial fibrillation [9].

The authors share the opinion that older age may be associated with more severe strokes due to the reduced functional capacity of endothelial cells and astrocytes following brain damage. With increasing age, a physiological decrease in cerebral blood flow occurs and this potentially affects neuronal damage after stroke in the elderly.

As a consequence, impaired cerebral circulation and subsequent neurological dysfunction may lead to more severe strokes and poorer recovery in older adults experiencing stroke. In addition, the authors also address the correlation between the severity of stroke in women and their poorer pre-stroke functional limitation in relation to age and several cardiovascular comorbidities (such as AF, hypertension, diabetes mellitus) as pre-stroke conditions.

Poor physical activity and conditions such as frailty, which is more common in women, affect the underlying biological mechanisms, including chronic inflammation, thus playing an important role in the pathogenesis of stroke and the severity of brain tissue damage.

Conclusion

Stroke remains one of the leading causes of death and disability in Europe, and projections show that with the "business as usual" approach, the burden of stroke is expected to remain high and will not be decreasing in the following decade. An important contributing factor is the increasing number of elderly in Europe, with projected increase of 35% between 2017 and 2050 [10].

Luckily, there is a convincing evidence that stroke can be prevented, treated, and there is a potential for drastic decrease of the stroke-related burden and its long lasting consequences.

Additional research is needed, covering the potential biological and clinical mechanisms, which would explain the severity of the consequences following between males and females, correlating their age and risk factors, in order to develop appropriate strategies regarding prevention and treatment of stroke.

References
1. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 2016;388:761–775.
2. GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1345–1422.
3. Stevens E, McKevitt C, Emmett E, et al. The burden of stroke in Europe. London: Stroke Alliance for Europe.(SAFE),2017.
4. Bushnell C, McCullough LD, Awad IA et al.; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. doi: 10.1161/01.str.0000442009.06663.48
5. Fromm A, Waje-Andreassen U, Thomassen L, Naess H. Comparison between Ischemic Stroke Patients <50 Years and ≥50 Years Admitted to a Single Centre: The Bergen Stroke Study. Stroke Res Treat. 2011 Jan 20; 2011:183256.

6. Crimmins EM, Shim H, Zhang YS, Kim JK. Differences between Men and Women in Mortality and the Health Dimensions of the Morbidity Process. Clin Chem. 2019 Jan;65(1):135-145. doi: 10.1373/clinchem.2018.288332.
7. SantaluciaP, Pezzella FR, Sessa M, Monaco S, Torgano G et al. Sex differences in clinical presentation, severity and outcome of stroke: Results from a hospital-based registry, European Journal of Internal Medicine,Volume 24, Issue 2, 2013, Pages 167-171.
8. Fromm, A, Waje-Andreassen, U, Thomassen, L Comparison between Ischemic stroke patients <50 years and ≥50 years admitted to a single centre: The Bergen Stroke Study. Stroke Res Treat 2011; 2011: 183256.
9. Phan HT, Reeves MJ, Blizzard CL, Thrift AG, Cadilhac DA et al. Sex Differences in Severity of Stroke in the INSTRUCT Study: a Meta-Analysis of Individual Participant Data. J Am Heart Assoc. 2019 Jan 8;8(1):e010235. doi: 10.1161/JAHA.118.010235.
10. Norrving B, Barrick J, Davalos A, Dichgans M, Cordonnier Cet al. Action Plan for Stroke in Europe 2018-2030. Eur Stroke J. 2018 Dec;3(4):309-336. doi: 10.1177/2396987318808719.