Gender and age differences in ischemic stroke in a hospital in Uberlândia, Brazil between 2011 and 2015

Diferenças entre os sexos e faixas etárias na epidemiologia acidentes vasculares cerebrais isquêmicos em um hospital de Uberlândia entre 2011 e 2015

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ABSTRACT: Ischemic stroke occurs when a cerebral artery is obstructed by a thrombus, an embolus, or compression from surrounding tissues. Ischemic strokes account for 80-87% of strokes. Strokes are the second leading cause of death worldwide and of natural deaths in men and women in Brazil. There are, however, few studies on the profile of ischemic stroke in cities such as Uberlândia, which is located in the interior of Brazil. The objective of this study is, thus, to describe the ischemic stroke profile in a Hospital in Uberlandia, between 2011-2015, with respect to gender and age group. This is a cross-sectional study. Only ischemic strokes were taken into account. All events resulting from hemorrhagic causes were excluded. This study observed that ischemic stroke followed a different pattern according to gender and age group. Regarding gender, this vascular event was slightly more prevalent in women. Regarding age group, up to age 70, ischemic stroke was predominant in men. After 70, however, it became predominant in women. This pattern was similar to the prevalence in age group of the following modifiable risk factors: hypertension, atrial fibrillation, type 2 diabetes mellitus, and tobacco use. This epidemiological understanding brings us closer to the real context of ischemic stroke in our population, underlining the need for individualized attention to the groups which this study shows to be most affected.

Keywords: Stroke/epidemiology; Ischemia/epidemiology; Age groups; age and sex distribution; Risk factors; Brazil/epidemiology.

RESUMO: Os Acidentes vasculares cerebrais isquêmicos (AVCI) ocorrem pela obstrução de uma artéria cerebral por um trombo, êmbolo ou compressão mecânica por tecidos circundantes. Os AVCI respondem por 80-87% dos Acidentes Vasculares Cerebrais (AVC). Essa etiologia é a segunda maior causa de morte no mundo e de óbitos naturais em homens e mulheres no Brasil. Entretanto, existem poucos estudos sobre o perfil dos AVCI em cidades interioranas do país como Uberlândia. Nesse sentido, o objetivo desse trabalho é descrever o perfil de AVCI em um Hospital de Uberlândia entre 2011-2015 por sexo e faixa etária. Trata-se de um estudo transversal. Foi considerado apenas esse tipo de AVC, excluindo os eventos por causas hemorrágicas. Esse estudo observou que o AVCI se comporta de maneira diferente de acordo com o sexo e faixa etária. Quanto ao sexo, esse evento vascular foi levemente mais prevalente em mulheres. Quanto à faixa etária, até os 70 anos, o AVCI predominou em homens. Após essa idade, as mulheres passaram a liderar. Esse padrão foi semelhante à prevalência por faixa etária dos seguintes fatores de risco modificáveis: hipertensão, fibrilação atrial, *diabetes mellitus* tipo 2 e tabagismo. O conhecimento dessa epidemiologia nos oferece uma maior proximidade ao real contexto do AVCI em nosso meio, refletindo a necessidade de uma atenção individualizada aos grupos mais acometidos mostrados nesse estudo.

Descritores: Acidente vascular cerebral/epidemiologia; Isquemia/epidemiologia; Grupos etários; Distribuição por idade e sexo; Fatores de risco; Brasil/epidemiologia.

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INTRODUCTION

Ischemic stroke is a neurological deficit caused when a cerebral artery is obstructed by a thrombus, an embolus, or compression from surrounding tissues. If this condition lasts for a few minutes, it may evolve into an infarct, leading to neurological death in the ischemic region[1].

Strokes are the second leading cause of death worldwide[2-5]. They are the fourth most prevalent cause of mortality in the United States, with an annual incidence of 700,000 cases (165,000 of which account for deaths) and respective annual costs reaching approximately 58 billion dollars[6-7]. In 2010, this vascular event was the second leading cause of natural death in men and women in Brazil, which is the country with the highest stroke mortality in Latin America[8-10]. Both in 2000 and in 2009, stroke affected women more than men[11]. Even though stroke's mortality index has declined in recent years, it continues to be high[8,12-15].

Ischemic stroke is the most prevalent type of stroke. Between 80 and 87% of strokes are ischemic. Stroke is a substantial cause of functional disability and mortality. Furthermore, strokes reduce patient quality of life and provoke significant impacts on family members[16-17].

Risk factors are classified as modifiable or non-modifiable[18-20]. The main modifiable risk factors are: hypertension, atrial fibrillation, diabetes mellitus, tobacco use, and dyslipidemia[21-28], and the main non-modifiable risk factors are: gender, age, heredity, and geographical location[18-19]. Males and blacks are the most susceptible groups. The risk of stroke mortality increases after age 60 and doubles with each successive decade[29-33]. In a study undertaken at the University of São Paulo School of Medicine, the average age of stroke patients admitted to the neurology ward was 53.4±16.4 years, and 62.3% of patients were men[34].

Atrial fibrillation (AF) is one of the leading causes of ischemic stroke. It occurs in 0.12-0.16% of individuals under age 49, in 3.7-4.2% of individuals between ages 60 and 70, and in 10-17% of individuals over age 80[35]. Independently, the presence of AF is associated with a five- to six-fold increase in risk of ischemic stroke[36-38]. Its prevalence increases significantly with age, being more common yet in patients with concomitant cardiovascular disease.

Systemic arterial hypertension (SAH) affects approximately 30% of the world's population[41]. It is the main modifiable risk factor of ischemic stroke[40-43]. According to the World Health Organization (WHO), 62% of all strokes can be attributed to elevated blood pressure levels[41,44]. In general, the higher a patient's blood pressure is, the higher his or her risk of ischemic stroke will be. This is true even for patients who do not have hypertension. As soon as blood pressure levels go above 115/75 mmHg, the risk of ischemic stroke increases linearly[44]. A series of clinical trials is currently documenting a decrease in ischemic stroke risk associated with pharmacological treatment of SAH in patients with elevated blood pressure levels[40-41].

Diabetes mellitus (DM) is another risk factor associated with ischemic stroke. This is due both to its participation in the pathophysiology of cerebrovascular diseases and to its significant epidemiological relevance which has made it a public health issue[40-41,45-46]. As many as 65% of patients who had at least one ischemic stroke episode were using dos hypoglycemic agents[45]. The relative risk of a diabetes patient developing a stroke varies between 1.8 and 6, with DM being associated with more negative prognoses (hyperglycemia in the context of cerebrovascular disease causes the ischemic penumbra to increase in area and increases the post-stroke mortality rate) and with an increased risk of developing subsequent ischemic events[47]. Diabetes milletus contributes to approximately 25% of stroke cases[45].

This study's objective is to describe the impact of age and gender in ischemic stroke patients at a hospital in Uberlândia between 2011 and 2015 and to correlate these aspects to risk factors.

METHODS

This is a cross-sectional study carried out with data retrieved from medical records from ischemic stroke admissions to the *Hospital das Clínicas in Uberlândia*. The sample period was five years (2011-2015). All medical records from this period were reviewed. The diagnosis of ischemic stroke was given by the attending physician based on anamnesis, physical examination, and imaging tests. Medical record forms that were not completely filled out were excluded from analysis. Only ischemic strokes were considered. All hemorrhagic events were excluded. Ischemic strokes were described according to gender and age group most affected within the two groups (male and female).

This study made use of primary data and data collection was carried out by the institution itself, in accordance with the institution's current protocol in effect. This study does not in any way present risks to the patients. For this reason, the need to obtain free and informed consent forms was waved. The Ethics Council of the institution recognized that the study does not cause any risks to participants, in accordance with Local Committee Resolution 510, Article 1, Paragraph III, ratified April 2016.

RESULTS

Women were most affected by ischemic stroke, as shown in Figure 1. This group represented 52% of cases admitted to the hospital. Men represented 48% of

ischemic events. Although the number of events is higher in men in all age groups up to 70, as shown in Figure 2, the numerical ratio between men in women over 70 was rather exacerbated, especially in patients over 80. This higher ratio in women exceeded all the event ratios which had been higher among men up to 70.
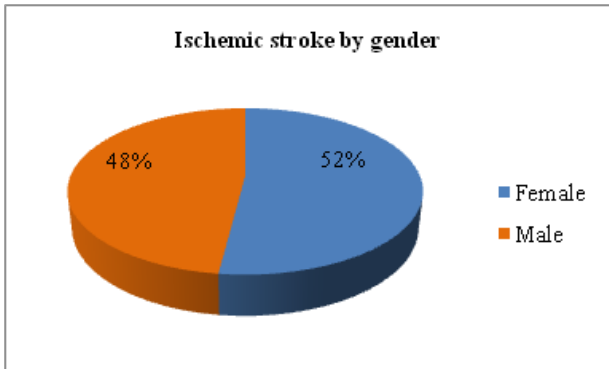
Figure 1. Percentage of ischemic stroke by gender in a hospital in Uberlândia, Brazil between 2011 and 2015
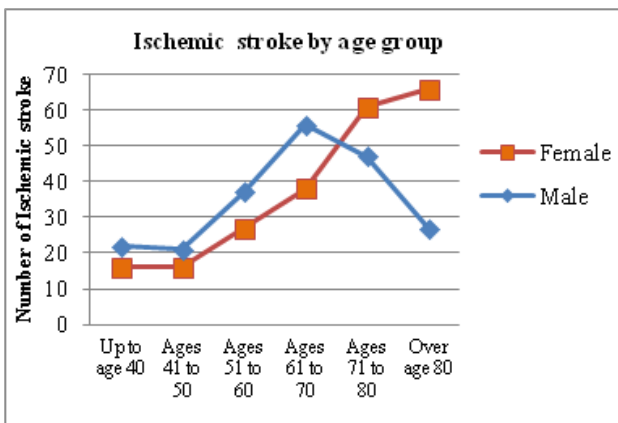
Figure 2. Ischemic stroke by age group in patients admitted to a hospital in Uberlândia, Brazil between 2011 and 2015

The ischemic vascular event pattern varies according to age, as shown in Figure 2. After age 50, the number of ischemic strokes increases drastically. In both sexes, the number of ischemic strokes observed during the first four decades of life is equivalent to the number observed only in the decade between 41 and 50 years of age. Between ages 51 and 70, the number of events increases progressively, and the numerical difference in ischemic strokes by gender is accentuated, being predominant in men. After the seventh decade of life, women take the numerical lead, with an accentuated difference starting after the eighth decade of life. Ultimately, overall predominance was found in women. The number of ischemic events after age 80 was four times greater in women than in men. In men, the mean age was 68.9 years, whereas in women the mean age was 71.5 years.

DISCUSSION

In this study, the overall percentage of ischemic stroke in women was slightly higher than in men. This can be explained by the accentuated predominance in events among women over 80. After age 80, women were four times more affected by stroke than men were. The higher life expectancy of women contributes to this occurrence profile being later in comparison with men. This, consequently, increases exposure[29]. In 2010, men's and women's life expectancy in Brazil were 70.5 and 77.7 years of age, respectively[10]. This higher life expectancy increases women's chances of developing or aggravating risk factors for ischemic stroke. The mean age for ischemic stroke obtained in this study was 68.9 for men and 71.5 for women. A systematic review conducted by the American Heart Association (AHA) obtained a mean age of 68.6 for men and 72.9 for women[30]. A study carried out in France observed a mean age of 66.1 and 70.6 for men and women, respectively[31]. Therefore, higher life expectancy may be the main explanation for the increase in exposure among women after the seventh and eighth decade of life and for the later mean occurrence of ischemic stroke.

There is a similarity between the prevalence of modifiable risk factors by age group and gender found in other studies and the distribution of ischemic stroke analyzed in this study. Freitas et al.[49] noted that hypertension is more prevalent in men only up to the fifth decade of life. The subsequent inversion (similar to that shown in Figure 2) after the fifth decade of life is mainly attributed to menopause[50]. After the sixth decade of life, the percentage of ischemic stroke cases reaches its peak in the ratio of prevalence between men and women. Atrial fibrillation is another important risk factor for ischemic stroke, which increases its prevalence with age[51]. Given that women's life expectancy is higher, this association is more accentuated in this gender and may be associated with the prevalence pattern recorded in this study. The attributable risk associating atrial fibrillation and ischemic stroke increases from 1.5% between ages 50 and 59 to 23.5% between ages 80 and 89, in both sexes[52,53]. This corresponds to the progressive increase in the number of ischemic strokes by decade, as shown in Figure 2. Type 2 diabetes mellitus is also a modifiable risk factor with a different pattern over age groups in both sexes. A cohort study[54] carried out in Japan observed that the incidence of type 2 diabetes mellitus is higher among men than among women, and that this metabolic disorder later in women than in men. In this way, type 2 diabetes mellitus is another factor that contributes to women being affected by ischemic stroke later, as found in this study. On the other hand, tobacco use is more prevalent in men than in women in all age groups, generally as early as adolescence[55]. This also predisposes men to be affected by ischemic stroke earlier in life than in women, as shown in Figure 2.

CONCLUSION

This study observed that ischemic stroke behaves differently according to gender and age group. Regarding gender, this vascular event was slightly more prevalent in women. Regarding age group, up to age 70, ischemic strokes were more common among men. After this age, they became more common in women. This pattern was similar to the age group prevalence of the following modifiable risk factors: hypertension, atrial fibrillation, type 2 diabetes mellitus, and tobacco use.

Contribution the autors: *Mateus de Sousa Rodrigues* - participated in the following phases: conceptualization, writing, visualization, reviewing, editing, and submission. *Leonardo Fernandes e Santana* - participated in the following phases: writing, reviewing, editing, and submission. *Daniel Borges Leal* - participated in the following phases: reviewing, editing, and submission. *Orlando Vieira Gomes* - provided supervision during all phases.

REFERENCES

1. Longo DL, et al. Medicina interna de Harrison. 18a ed. Porto Alegre: AMGH; 2013. 2v, p.3270-98.

2. Cabral NL. Avaliação da incidência, mortalidade e letalidade por doenças cerebrovascular em Joinville, Brasil: comparação entre o ano de 1995 e o período de 2005-6 [tese]. São Paulo: Universidade de São Paulo; 2008. doi: 10.11606/T.5.2008. tde-29012009-144258.

3. Lavados PM, Hennis AJ, Fernandes JG, Medina MT, Legetic B, Hoppe, et al. AVC epidemiology, prevention, and management strategies at a regional level: Latin America and the Caribbean. Lancet Neurol. 2007;6(4):362-72. doi: 10.1016/S1474-4422(07)70003-0.

4. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355-69. doi: 10.1016/S1474-4422(09)70025-0.

5. Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modeling. Lancet Neurol. 2009;8(4):345-54. doi: 10.1016/S1474-4422(09)70023-7.

6. Maitin IB. Current: medicina física e reabilitação: diagnóstico e tratamento. Porto Alegre: AMGH; 2016.

7. Leite HR, Nunes APN, Corrêa CL. Perfil epidemiológico de pacientes acometidos por acidente vascular encefálico cadastrados na Estratégia de Saúde da Família em Diamantina, MG. Fisioter Pesqui. 2009;16(1):34-9. http://dx.doi.org/10.1590/S1809-29502009000100007.

8. Lotufo PA, BensenorIM. Stroke mortality in São Paulo (1997-2003): a description using the Tenth Revision of the International Classification of Diseases. Arq Neuropsiquiatr. 2004;62(4):1008-11. http://dx.doi.org/10.1590/S0004-282X2004000600014.

9. Lotufo PA. Stroke in Brazil: a neglected disease. São Paulo Med J. 2005;123(1):3-4. http://dx.doi.org/10.1590/S1516-31802005000100001.

10. Marinho F, Passos VM de A, França EB. Novo século, novos desafios: mudança no perfil da carga de doença no Brasil de 1990 a 2010. Epidemiol Serv Saúde. 2016;25(4):713-24. http://dx.doi.org/10.5123/s1679-49742016000400005.

11. Pan American Health Organization - PAHO. Causas principales de mortalidad [Citado 01 jan. 2016]. Disponível em: http://ais.paho.org/phip/viz/mort_causasrpincipales.

12. Andre C, Curioni CC, Braga da Cunha C, Veras R. Progressive decline in stroke mortality in Brazil from 1980 to 1982, 1990 to 1992, and 2000 to 2002. Stroke. 2006;37(11):2784-9. doi: 10.1161/01.STR.0000244768.46566.73

13. Cabral NL, Gonçalves AR, Longo AL, Moro CH, Costa G, Amaral CH, et al. Trends in stroke incidence, mortality and case fatality rates in Joinville, Brazil: 1995-2006. J Neurol Neurosurg Psychiatry. 2009;80(7):749-54. doi: 10.1136/jnnp.2008.164475.

14. Mansur Ade P, Favarato D, Avakian SD, Ramires JA. Trends in ischemic heart disease and stroke death ratios in brazilian women and men. Clinics. 2010;65(11):1143-7. http://dx.doi.org/10.1590/S1807-59322010001100016.

15. Garritano CR, Luz PM, Pires MLE, et al. Análise da tendência da mortalidade por acidente vascular cerebral no Brasil no século XXI.Arq Bras Cardiol. 2012;98(6):519-27. http://dx.doi.org/10.1590/S0066-782X2012005000041.

16. Della-Morte D, Guadagni F, Palmirotta R, Testa G, et al. Genetics of ischemic stroke, stroke-related risk factors, stroke precursors and treatments. Pharmacogenomics. 2012;13(5):595-613. doi: 10.2217/pgs.12.14.

17. De Lavor IG, Agra G, Nepomuceno CM. Perfil dos casos de acidente vascular cerebral registrados em uma instituição pública de saúde em Campina Grande – PB. Revista Tema (Campina Grande). 2011;12(17). Disponível em: http://revistatema.facisa.edu.br/index.php/revistatema/article/view/88/105

18. Tayal AH, Tian KM, Kelly M, et al. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. Neurology. 2008;71:1696-701. doi: 10.1212/01.wnl.0000325059.86313.31.

19. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. Stroke. 2004;35:1647-51. doi: 10.1161/01.STR.0000131269.69502.d9.

20. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics – 2012 update: a report from the American Heart Association. Circulation. 2012;125:e2-e220. doi: 10.1161/CIR.0b013e31828124ad.

21. Adams RJ, Albers G, Albers MJ. Update to the AHA/ASA

recommendations for the prevention of stroke in patients with stroke and ischemic attack. Stroke. 2008;39:1647-1652. doi: 10.1161/STROKEAHA.107.189063.

22. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, Khatiwoda A, Lisabeth L. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. Lancet Neurol. 2008;7:915-26. doi: 10.1016/S1474-4422(08)70193-5.

23. Andersen KK, Andersen ZJ, Olsen TS. Age- and gender-specific prevalence of cardiovascular risk factors in 40,102 patients with first-ever ischemic stroke: a Nationwide Danish Study. Stroke. 2010;41:2768-74. doi: 10.1161/STROKEAHA.110.595785.

24. Tsang TS, Petty GW, Barnes ME, O'Fallon WM, Bailey KR, Wiebers DO, Sicks JD, Christianson TJ, Seward JB, Gersh BJ. The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: changes over three decades. J Am Coll Cardiol. 2003;42:93-100. https://doi.org/10.1016/S0735-1097(03)00500-X.

25. Perkin GD. Atlas Mosby em cores e texto de neurologia. Trad. Rosângela Santoro de Souza. São Paulo: Manole; 1998. p. 109-110.

26. Collins R, Armitage J, Parish S, et al. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular desease or other hogh-risk conditions. Lancet. 2004;363:757-767. DOI: 10.1016/S0140-6736(04)15690-0

27. Timaran CH, Mantese VA, Malas M, et al. Differential outcomes of carotid stenting and endarterectomy performed exclusively by vascular surgeons in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). J Vas Surg. 2013;57:303-308. doi: 10.1016/j.jvs.2012.09.014.

28. Wang Y, Wang W, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke on transient ischemic attack. N Eng J Med. 2013;369; 11-19. doi: 10.1056/NEJMoa1215340.

29. Rojas JL, Zurrú MC, Romano M, Patrucco L, Cristiano E. Acute ischemic stroke and transient ischemic attack in the very old – risk factor profile and stroke subtype between patients older than 80 years and patients aged less than 80 years. Eur J Neurol. 2007;14(8):895-9. doi: 10.1111/j.1468-1331.2007.01841.x.

30. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a systematic review. Stroke. 2009;40(4):1082-90. doi: 10.1161/STROKEAHA.108.540781.

31. Moulin T, Tatu L, Crépin-Leblond T, Chavot D, Bergés S, Rumbach T. The Besançon Stroke Registry: an acute stroke registry of 2,500 consecutive patients. Eur J Neurol. 1997;38(1):10-20. doi: 10.1159/000112896.

32. De Castro JAB, Epstein MG, Sabino GB, et al. Estudo dos principais fatores de risco para acidente vascular encefálico. Rev Bras Clin Med. 2009;7:171-3. Disponível em: http://files.bvs.br/upload/S/1679-1010/2009/v7n3/a171-173.pdf.

33. Rolim CLRC, Martins M. Qualidade do cuidado ao acidente vascular cerebral isquêmico no SUS. Cad Saúde Pública (Rio de Janeiro). 2011;27(11):2106-16. http://dx.doi.org/10.1590/S0102-311X2011001100004.

34. De Paulo RB, Guimarães TM, Helito PVP, et al. Acidente vascular cerebral isquêmico em uma enfermaria de neurologia: complicações e tempo de internação. Rev Assoc Med Bras. 2009;55(3):313-6. http://dx.doi.org/10.1590/S0104-42302009000300025.

35. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014:213-9. doi: 10.2147/CLEP.S47385.

36. Friberg L, Rosenqvist M, Lindgren A, Terént A, Norrving B, Asplund K. High prevalence of atrial fibrillation among patients with ischemic stroke. Stroke. 2014;45(9):2599-605. doi: 10.1161/STROKEAHA.114.006070.

37. Buchwald F, Norrving B, Petersson J. Atrial fibrillation in transient ischemic attack versus ischemic stroke. A Swedish Stroke Register (Risk stroke) Study. Stroke. 2016;47(10):2456-61. doi: 10.1161/STROKEAHA.116.013988. .

38. Joundi RA, Cipriano LE, Sposato LA, Saposnik G, Stroke Outcomes Research Working Group. Ischemic Stroke Risk in Patients With Atrial Fibrillation and CHA_2DS_2-VASc Score of 1. Stroke. 2016;47(5):1364-7. doi: 10.1161/STROKEAHA.115.012609.

39. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. J Intern Med. 2013;274(5):461-8. doi: 10.1111/joim.12114

40. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA; American Heart Association Stroke Council; et al. Guidelines for the Primary Prevention of stroke: a statement for healthcare professionals from the American Heart Association. Stroke. 2014;45(12):3754-832. doi: 10.1161/STR.0000000000000046.

41. Soler EP, Ruiz VC.. Epidemiology and risk factors of cerebral ischemia and ischemic heart diseases: similarities and differences. Curr Cardiol Rev. 2010;6(3):138-49. doi: 10.2174/157340310791658785.

42. McManus M, Liebeskind DS. Blood Pressure in Acute Ischemic Stroke. J Clin Neurol. 2016;12(2):137-46. doi: 10.3988/jcn.2016.12.2.137.

43. Arboix A. Cardiovascular risk factors for acute stroke: risk profiles in the different subtypes of ischemic stroke. World J Clin Cases. 2015;3(5):418-29. doi: 10.12998/wjcc.v3.i5.418.

44. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. et al. Prospective Studies Collaboration. Age-specific relevance of usualblood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.

45. Al-Rubeaan K, Al-Hussain F, Youssef AM, Subhani SN, Al-Sharqawi AH, Ibrahim HM. Ischemic stroke and its risk factors in a registry-based large cross-sectional diabetic cohort in a country facing facing a diabetes epidemic. J Diabetes Res. 2016;2016:4132589. doi: 10.1155/2016/4132589.

46. Khoury JC, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, Broderick JP,

Kissela BM. Diabetes: a risk factor for ischemic stroke in a large bi-racial population. Stroke. 2013;44(6):1500-4. doi: 10.1161/STROKEAHA.113.001318.

47. Romero JR, Morris J, Pikula A. Stroke prevention: modifying risk factors. Ther Adv Cardiovasc Dis. 2008;2(4):287-303. doi: 10.1177/1753944708093847.

48. Zhang Z, Yan J, Shi H. Hyperglycemia as a risk factor of ischemic stroke. J Drug Metab Toxicol. 2013;4(4).pii:153. doi: 10.4172/2157-7609.1000153.

49. Freitas LRS, Garcia LP. Evolution of prevalence of diabetes and associated hypertension in Brazil: analysis of National Household Sample Survey, 1998, 2003 and 2008. Epidemiol Serv Saúde [Brasília]. 2012;21(1):7-19. Disponível em: http://scielo.iec.gov.br/pdf/ess/v21n1/v21n1a02.pdf.

50. Buleishvili M, Lobjanidze N, Ormotsadze G, Enukidze M, Machavariani M, SanikidzeT. Estrogen related mechanisms of hypertension in menopausal women. Georgian Med News. 2016;(255):45-51.

51. Naderi S, Wang Y, Miller AL, et al. The impact of age on the epidemiology of atrial fibrillation hospitalizations. Am J Med. 2014;127(2):158.e1-158.e7. doi:10.1016/j.amjmed.2013.10.005.

52. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22:983-8. https://doi.org/10.1161/01.STR.22.8.983.

53. Renoux C, Patenaude V, Suissa S. Incidence, mortality, and sex differences of non-valvular atrial fibrillation: a population-based study. J Am Heart Assoc. 2014;3(6):e001402. doi:10.1161/JAHA.114.001402.

54. Murakata Y, Fujimaki T, Yamada Y. Age-related changes in clinical parameters and their associations with common complex diseases. Biomed Rep. 2015;3(6):767-77. doi:10.3892/br.2015.505.

55. Harris JK, Geremakis C, Moreland-Russell S, Carothers BJ, Kariuki B, Shelton SC, Kuhlenbeck M. Demographic and geographic differences in exposure to secondhand smoke in Missouri workplaces, 2007-2008. Prev Chronic Dis. 2011;8(6):A135. Available from: http://www.cdc.gov/pcd/issues/2011/nov/10_0197.htm.