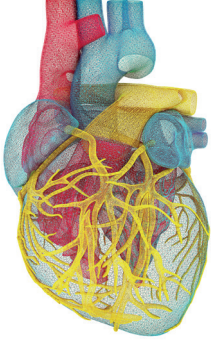


BÖLÜM 40



Diyabetik Hastada Serebrovasküler Hastalık

Gökçe AYHAN ARSLAN ¹

| GİRİŞ

Serebrovasküler hastalıklar, dünya çapında mortalite ve erişkin morbiditesinin ikinci önde gelen nedeni olarak kabul edilen önemli bir halk sağlığı sorunudur (1, 2). Tüm inmelerin %87'sini iskemik inmeler, %10'unu intraserebral kanamalar (İSK), %3'ünü ise subaraknoid kanamalar oluşturur (3). Diyabet, nörovasküler hastalıklar için iyi bilinen bir risk faktörüdür (4-6). Diyabetik hastalarda inme riski her yıl %3 artmakta olup, 10 yıldan fazla diyabetik olan hastalarda ise bu risk üçe katlanmaktadır (7).

Benzer şekilde Tip 2 diyabetes mellitus (DM) da serebrovasküler hastalık için belirlenmiş bir risk faktörüdür (8, 9). Kohort çalışmalarında, Tip 2 DM diğer risk faktörlerinden bağımsız olarak hem iskemik hem de hemorajik inme için yüksek risk ile ilişkilidir (10). Tip 2 diyabet tek başına inme riskini 1.5 - 4 kat artırmakla birlikte olumsuz klinik sonlanıma neden olur. (11). Ayrıca, akut inme nedeniyle başvuran hastaların yaklaşık % 20-33'ünün diyabetik olduğu tahmin edilmektedir (5, 12).

Yaklaşık 8,5 milyon diyabetik hastanın izlendiği 102 prospektif çalışmanın değerlendirildiği bir meta-analiz çalışmasında iskemik inme riskinin 2.27 ve hemorajik inme riskinin ise 1.56 kat arttığı gösterilmiştir (10). Diyabet ayrıca geçici iskemik atak (GİA) sonrası inme riskini de artırır ve ABCD2 GİA risk skorlamasına dahildir (13).

Diyabet ve inme riski ilişkisi cinsiyete göre farklılık göstermektedir. Majör kardiyovasküler risk faktörlerindeki temel farklılıklar dikkate alınarak diyabetik erkeklerle karşılaştırıldığında, diyabetik kadınlardaki diyabetik inme rölatif riskinin %27 daha fazla olduğu bildirilmiştir (14).

Diyabet, inme rekürrensi için de bağımsız bir risk faktörüdür. Daha önce inme geçirmiş katılımcıları içeren 18 çalışmanın meta-analiz sonucuna göre diyabetik hastalarda diyabetik olmayanlara göre daha yüksek inme rekürrensi tespit edilmiştir (15). İnme rekürrens riskinin artışıyla birlikte (16) diyabet, özellikle inmeden sonra ortaya çıkan kognitif bozukluk ve demans gelişme riskinin riskini artırmaktadır.(17).

¹ Uzm. Dr., Erciş Şehit Rıdvan Çevik Devlet Hastanesi, Nöroloji Kliniği, gokce_ayhan@yahoo.com.tr

Yakın zamanda yayınlanan bir meta-analizde diyabetik hastalarda düşük doz ASA kullanımı (≤ 100 mg/gün) ile inme riskinde önemli ölçüde azalma gösterilmiştir (76). Başka bir meta-analizde ise iskemik inmenin primer önlenmesinde ASA kullanımının rölatif riski %10 azalttığı tespit edilmiştir (77). Ancak, inmenin primer ve sekonder önlenmesinde antiagregan temelli tedavi planını belirlenirken kanama riski göz önünde bulundurulmalıdır (78).

Diyabet hastalarında sistolik kan basıncının 10 mmHg düşmesi inme riskini azaltmaktadır. Sistolik kan basıncının düşürülmesi, bazal sistolik kan basıncı ≥ 140 mm Hg olan tip 2 diyabet hastalarında inme riskini azaltmaktadır. Öte yandan, sistolik kan basıncının 130 mm Hg'nin altına düşürülmesi daha düşük inme riski ile ilişkilidir ve bu durum, yüksek inme riski olan bireylerde daha yoğun kan basıncını düşürmenin faydalı olduğunu göstermektedir (79).

Yeni nesil antidiyabetik ajanlarla ilgili yakın zamanda yapılan bir meta-analizde pioglitazon ve ayrıca GLP-1RA sınıfı ilaçların diyabeti veya insulin direnci olan hastalarda doğrudan glukoz düşürmeyen mekanizmalarla inme riskini azalttığı gösterilmiştir (80).

SONUÇ

Rehberler doğrultusunda akut iskemik inmeden sonra tüm hastaların DM açısından açlık plazma glukozu, HbA1c veya oral glukoz tolerans testiyle taranması önerilmektedir. Genel olarak, inme sonrasındaki erken dönemde HbA1c ile değerlendirme diğer testlerden daha doğru sonuç verebilmektedir. Diyabet hastalarında inmenin primer ve sekonder önlenmesinde tedavi modaliteleri belirlenirken artmış kanama riski göz önünde bulundurulmalı ve bireysel olarak fayda-zarar oranı belirlenerek tedavi planlanmalıdır. Ayrıca diyabetik hastalarda kısa ve uzun dönemdeki olumsuz etkileri düşünüldüğünde hipoglisemiden kaçınılmalıdır. İnmenin önlenmesinde bütüncül yaklaşım önemli olup mevcut komorbid durumların tedavisi ve yaşam tarzı değişikliği yapılması önemlidir.

KAYNAKLAR

1. Kassebaum NJ, Arora M, Barber RM, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1603-58.DOI: 10.1016/s0140-6736(16)31460-x.
2. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459-544. DOI: 10.1016/s0140-6736(16)31012-1.
3. Tsoo CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. *Circulation*. 2022;145(8):e153-e639.DOI: 10.1161/cir.0000000000001052.
4. Cavender MA, Scirica BM, Raz I, et al. Cardiovascular Outcomes of Patients in SAVOR-TIMI 53 by Baseline Hemoglobin A1c. *The American journal of medicine*. 2016;129(3):340.e1-8.DOI: 10.1016/j.amjmed.2015.09.022.
5. 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(10046):761-75.DOI: 10.1016/s0140-6736(16)30506-2.
6. Hu G, Jousilahti P, Sarti C, et al. The effect of diabetes and stroke at baseline and during follow-up on stroke mortality. *Diabetologia*. 2006;49(10):2309-16.DOI: 10.1007/s00125-006-0378-1.
7. Banerjee C, Moon YP, Paik MC, et al. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. *Stroke*. 2012;43(5):1212-7.DOI: 10.1161/strokeaha.111.641381.
8. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *European heart journal*. 2020;41(2):255-323.DOI: 10.1093/eurheartj/ehz486.
9. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(12):3754-832.DOI: 10.1161/str.0000000000000046.
10. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375(9733):2215-22.DOI: 10.1016/s0140-6736(10)60484-9.
11. Chen R, Ovbiagele B, Feng W. Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. *The American journal of the medical sciences*. 2016;351(4):380-6.DOI: 10.1016/j.amjms.2016.01.011.

12. Gray CS, Scott JF, French JM, et al. Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke. *Age and ageing*. 2004;33(1):71-7. DOI: 10.1093/ageing/afh026.
13. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet*. 2009;373(9677):1765-72. DOI: 10.1016/s0140-6736(09)60697-8.
14. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet*. 2014;383(9933):1973-80. DOI: 10.1016/s0140-6736(14)60040-4.
15. Shou J, Zhou L, Zhu S, et al. Diabetes is an Independent Risk Factor for Stroke Recurrence in Stroke Patients: A Meta-analysis. *Journal of stroke and cerebrovascular diseases*. 2015;24(9):1961-8. DOI: 10.1016/j.jstrokecerebrovasdis.2015.04.004.
16. Echouffo-Tcheugui JB, Xu H, Matsouaka RA, et al. Diabetes and long-term outcomes of ischaemic stroke: findings from Get With The Guidelines-Stroke. *European heart journal*. 2018;39(25):2376-86. DOI: 10.1093/eurheartj/ehy036.
17. Shang Y, Fratiglioni L, Marseglia A, et al. Association of diabetes with stroke and post-stroke dementia: A population-based cohort study. *Alzheimer's and dementia*. 2020;16(7):1003-12. DOI: 10.1002/alz.12101.
18. Kissela B, Air E. Diabetes: impact on stroke risk and poststroke recovery. *Seminars in neurology*. 2006;26(1):100-7. DOI: 10.1055/s-2006-933313.
19. Stephens JW, Khanolkar MP, Bain SC. The biological relevance and measurement of plasma markers of oxidative stress in diabetes and cardiovascular disease. *Atherosclerosis*. 2009;202(2):321-9. DOI: 10.1016/j.atherosclerosis.2008.06.006.
20. Béjot Y, Giroud M. Stroke in diabetic patients. *Diabetes and metabolism*. 2010;36 Suppl 3:S84-7. DOI: 10.1016/s1262-3636(10)70472-9.
21. Chen J, Cui X, Zacharek A, et al. White matter damage and the effect of matrix metalloproteinases in type 2 diabetic mice after stroke. *Stroke*. 2011;42(2):445-52. DOI: 10.1161/strokeaha.110.596486.
22. Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. *Hypertension*. 2005;46(5):1118-22. DOI: 10.1161/01.HYP.0000185463.27209.b0.
23. Roher AE, Esh C, Kokjohn TA, et al. Circle of willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arteriosclerosis, thrombosis, and vascular biology*. 2003;23(11):2055-62. DOI: 10.1161/01.Atv.0000095973.42032.44.
24. Moreno PR, Fuster V. New aspects in the pathogenesis of diabetic atherothrombosis. *Journal of the American college of cardiology*. 2004;44(12):2293-300. DOI: 10.1016/j.jacc.2004.07.060.
25. Henry RM, Kostense PJ, Dekker JM, et al. Carotid arterial remodeling: a maladaptive phenomenon in type 2 diabetes but not in impaired glucose metabolism: the Hoorn study. *Stroke*. 2004;35(3):671-6. DOI: 10.1161/01.Str.0000115752.58601.0b.
26. Fang HJ, Zhou YH, Tian YJ, et al. Effects of intensive glucose lowering in treatment of type 2 diabetes mellitus on cardiovascular outcomes: A meta-analysis of data from 58,160 patients in 13 randomized controlled trials. *International journal of cardiology*. 2016;218:50-8. DOI: 10.1016/j.ijcard.2016.04.163.
27. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *The New England journal of medicine*. 2008;358(24):2545-59. DOI: 10.1056/NEJMoa0802743.
28. Gerstein HC, Beavers DP, Bertoni AG, et al. Nine-Year Effects of 3.7 Years of Intensive Glycemic Control on Cardiovascular Outcomes. *Diabetes care*. 2016;39(5):701-8. DOI: 10.2337/dc15-2283.
29. Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *The New England journal of medicine*. 2014;371(15):1392-406. DOI: 10.1056/NEJMoa1407963.
30. Reaven PD, Emanuele NV, Wiitala WL, et al. Intensive Glucose Control in Patients with Type 2 Diabetes - 15-Year Follow-up. *The New England journal of medicine*. 2019;380(23):2215-24. DOI: 10.1056/NEJMoa1806802.
31. Zhang C, Zhou YH, Xu CL, et al. Efficacy of intensive control of glucose in stroke prevention: a meta-analysis of data from 59,197 participants in 9 randomized controlled trials. *The public library of science one*. 2013;8(1):e54465. DOI: 10.1371/journal.pone.0054465.
32. Bellolio MF, Gilmore RM, Ganti L. Insulin for glycaemic control in acute ischaemic stroke. *The Cochrane database of systematic reviews*. 2014(1):Cd005346. DOI: 10.1002/14651858.CD005346.pub4.
33. Zheng D, Zhao X. Intensive Versus Standard Glucose Control in Patients with Ischemic Stroke: A Meta-Analysis of Randomized Controlled Trials. *World neurosurgery*. 2020;136:e487-e95. DOI: 10.1016/j.wneu.2020.01.042.
34. Bebu I, Schade D, Braffett B, et al. Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study. *Diabetes care*. 2020;43(4):867-74. DOI: 10.2337/dc19-2292.
35. Georgakis MK, Harshfield EL, Malik R, et al. Diabetes Mellitus, Glycemic Traits, and Cerebrovascular Disease: A Mendelian Randomization Study. *Neurology*. 2021;96(13):e1732-e42. DOI: 10.1212/wnl.00000000000011555.
36. Tsvigoulis G, Katsanos AH, Mavridis D, et al. Association of Baseline Hyperglycemia With Outcomes of Patients With and Without Diabetes With Acute Ischemic Stroke Treated With Intravenous Thrombolysis: A Propensity Score-Matched Analysis From the SITS-ISTR Registry. *Diabetes*. 2019;68(9):1861-9. DOI: 10.2337/db19-0440.

37. Fuentes B, Castillo J, San José B, et al. The prognostic value of capillary glucose levels in acute stroke: the GLyemia in Acute Stroke (GLIAS) study. *Stroke*. 2009;40(2):562-8. DOI: 10.1161/strokeaha.108.519926.
38. Miedema I, Luijckx GJ, Brouns R, et al. Admission hyperglycemia and outcome after intravenous thrombolysis: is there a difference among the stroke-subtypes? *BMC neurology*. 2016;16:104. DOI: 10.1186/s12883-016-0617-0.
39. Paciaroni M, Agnelli G, Caso V, et al. Acute hyperglycemia and early hemorrhagic transformation in ischemic stroke. *Cerebrovascular Diseases*. 2009;28(2):119-23. DOI: 10.1159/000223436.
40. Bruno A, Levine SR, Frankel MR, et al. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology*. 2002;59(5):669-74. DOI: 10.1212/wnl.59.5.669.
41. Fuentes B, Pastor-Yborra S, Gutiérrez-Zúñiga R, et al. Glycemic variability: prognostic impact on acute ischemic stroke and the impact of corrective treatment for hyperglycemia. The GLIAS-III translational study. *Journal of translational medicine*. 2020;18(1):414. DOI: 10.1186/s12967-020-02586-4.
42. Kaze AD, Santhanam P, Erqou S, et al, Echouffo-Tcheugui JB. Long-term variability of glycemic markers and risk of all-cause mortality in type 2 diabetes: the Look AHEAD study. *BMJ open diabetes research and care*. 2020;8(2). DOI: 10.1136/bmjdr-2020-001753.
43. Scott ES, Januszewski AS, O'Connell R, et al. Long-Term Glycemic Variability and Vascular Complications in Type 2 Diabetes: Post Hoc Analysis of the FIELD Study. *The journal of clinical endocrinology and metabolism*. 2020;105(10). DOI: 10.1210/clinem/dgaa361.
44. Hirakawa Y, Arima H, Zoungas S, et al. Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. *Diabetes care*. 2014;37(8):2359-65. DOI: 10.2337/dc14-0199.
45. Nusca A, Tuccinardi D, Albano M, et al. Glycemic variability in the development of cardiovascular complications in diabetes. *Diabetes/ Metabolism Research and Reviews*. 2018;34(8):e3047. DOI: 10.1002/dmrr.3047.
46. Egi M, Bellomo R, Stachowski E, et al. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology*. 2006;105(2):244-52. DOI: 10.1097/00000542-200608000-00006.
47. Nusca A, Tuccinardi D, Proscia C, et al. Incremental role of glycaemic variability over HbA1c in identifying type 2 diabetic patients with high platelet reactivity undergoing percutaneous coronary intervention. *Cardiovascular diabetology*. 2019;18(1):147. DOI: 10.1186/s12933-019-0952-8.
48. Mendez CE, Mok KT, Ata A, et al. Increased glycemic variability is independently associated with length of stay and mortality in noncritically ill hospitalized patients. *Diabetes care*. 2013;36(12):4091-7. DOI: 10.2337/dc12-2430.
49. Lim JS, Kim C, Oh MS, et al. Effects of glycemic variability and hyperglycemia in acute ischemic stroke on post-stroke cognitive impairments. *Journal of diabetes and its complications*. 2018;32(7):682-7. DOI: 10.1016/j.jdiacomp.2018.02.006.
50. Wada S, Yoshimura S, Inoue M, et al. Outcome Prediction in Acute Stroke Patients by Continuous Glucose Monitoring. *Journal of the American heart association*. 2018;7(8). DOI: 10.1161/jaha.118.008744.
51. Ye G, Gao Q, Qi P, et al. The role of diabetes mellitus on the thrombus composition in patients with acute ischemic stroke. *Interventional neuroradiology*. 2020;26(3):329-36. DOI: 10.1177/1591019919896940.
52. Yang X, Li C, Li J, et al. Insulin Resistance is Significantly Related with Worse Clinical Outcomes in Non-Diabetic Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis. *Journal of stroke and cerebrovascular diseases*. 2021;30(3):105526. DOI: 10.1016/j.jstrokecerebrovasdis.2020.105526.
53. Hao Z, Yang C, Xiang L, et al. Risk factors for intracranial hemorrhage after mechanical thrombectomy: a systematic review and meta-analysis. *Expert review of neurotherapeutics*. 2019;19(10):927-35. DOI: 10.1080/14737175.2019.1632191.
54. Desilles JP, Meseguer E, Labreuche J, et al. Diabetes mellitus, admission glucose, and outcomes after stroke thrombolysis: a registry and systematic review. *Stroke*. 2013;44(7):1915-23. DOI: 10.1161/strokeaha.111.000813.
55. Mishra NK, Davis SM, Kaste M, et al. Comparison of outcomes following thrombolytic therapy among patients with prior stroke and diabetes in the Virtual International Stroke Trials Archive (VISTA). *Diabetes care*. 2010;33(12):2531-7. DOI: 10.2337/dc10-1125.
56. Reiter M, Teuschl Y, Matz K, et al. Diabetes and thrombolysis for acute stroke: a clear benefit for diabetics. *European journal of neurology*. 2014;21(1):5-10. DOI: 10.1111/ene.12263.
57. Fang HJ, Pan YS, Wang YJ, et al. Prognostic value of admission hyperglycemia on outcomes of thrombolysis in ischemic stroke patients with or without diabetes. *Chinese medical journal (English)*. 2020;133(18):2244-6. DOI: 10.1097/cm9.0000000000001005.
58. Borggrefe J, Glück B, Maus V, et al. Clinical Outcome After Mechanical Thrombectomy in Patients with Diabetes with Major Ischemic Stroke of the Anterior Circulation. *World neurosurgery*. 2018;120:e212-e20. DOI: 10.1016/j.wneu.2018.08.032.
59. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418. DOI: 10.1161/str.0000000000000211.
60. Boulanger M, Poon MT, Wild SH, et al. Association between diabetes mellitus and the occurrence and outcome of intracerebral hemorrhage. *Neurology*. 2016;87(9):870-8. DOI: 10.1212/wnl.0000000000003031.

61. Saliba W, Barnett-Griness O, Gronich N, et al. Association of Diabetes and Glycated Hemoglobin With the Risk of Intracerebral Hemorrhage: A Population-Based Cohort Study. *Diabetes care*. 2019;42(4):682-8.DOI: 10.2337/dc18-2472.
62. Mohr JP, Kase CS, Meckler RJ, et al. Sensorimotor stroke due to thalamocapsular ischemia. *Archives of neurology*. 1977;34(12):739-41.DOI: 10.1001/archneur.1977.00500240027004.
63. Korf ES, van Straaten EC, de Leeuw FE, et al. Diabetes mellitus, hypertension and medial temporal lobe atrophy: the LADIS study. *Diabetic medicine*. 2007;24(2):166-71.DOI: 10.1111/j.1464-5491.2007.02049.x.
64. Vermeer SE, Koudstaal PJ, Oudkerk M, et al. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke*. 2002;33(1):21-5.DOI: 10.1161/hs0102.101629.
65. van Harten B, de Leeuw FE, Weinstein HC, et al. Brain imaging in patients with diabetes: a systematic review. *Diabetes care*. 2006;29(11):2539-48.DOI: 10.2337/dc06-1637.
66. Fazekas F, Kleinert R, Offenbacher H, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*. 1993;43(9):1683-9.DOI: 10.1212/wnl.43.9.1683.
67. Schmidt R, Schmidt H, Kapeller P, et al. The natural course of MRI white matter hyperintensities. *Journal of the neurological sciences*. 2002;203-204:253-7.DOI: 10.1016/s0022-510x(02)00300-3.
68. de Graaf RA, Pan JW, Telang F, et al. Differentiation of glucose transport in human brain gray and white matter. *Journal of cerebral blood flow and metabolism*. 2001;21(5):483-92.DOI: 10.1097/00004647-200105000-00002.
69. Del Bene A, Ciolli L, Borgheresi L, et al. Is type 2 diabetes related to leukoaraiosis? an updated review. *Acta neurologica scandinavica*. 2015;132(3):147-55.DOI: 10.1111/ane.12398.
70. Rastogi A, Weissert R, Bhaskar SMM. Emerging role of white matter lesions in cerebrovascular disease. *European journal of neuroscience*. 2021;54(4):5531-59.DOI: 10.1111/ejn.15379.
71. Arsava EM, Rahman R, Rosand J, et al. Severity of leukoaraiosis correlates with clinical outcome after ischemic stroke. *Neurology*. 2009;72(16):1403-10.DOI: 10.1212/WNL.0b013e3181a18823.
72. van Harten B, Oosterman J, Muslimovic D, et al. Cognitive impairment and MRI correlates in the elderly patients with type 2 diabetes mellitus. *Age and ageing*. 2007;36(2):164-70.DOI: 10.1093/ageing/afl180.
73. Hill MD. Stroke and diabetes mellitus. *Handbook of clinical neurology*. 2014;126:167-74.DOI: 10.1016/b978-0-444-53480-4.00012-6.
74. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9431):331-7.DOI: 10.1016/s0140-6736(04)16721-4.
75. Benavente OR, Hart RG, McClure LA, et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *The New England journal of medicine*. 2012;367(9):817-25.DOI: 10.1056/NEJMoa1204133.
76. Seidu S, Kunutsor SK, Sesso HD, et al. Aspirin has potential benefits for primary prevention of cardiovascular outcomes in diabetes: updated literature-based and individual participant data meta-analyses of randomized controlled trials. *Cardiovascular diabetology*. 2019;18(1):70.DOI: 10.1186/s12933-019-0875-4.
77. Gelbenegger G, Postula M, Pecen L, et al. Aspirin for primary prevention of cardiovascular disease: a meta-analysis with a particular focus on subgroups. *BMC medicine*. 2019;17(1):198.DOI: 10.1186/s12916-019-1428-0.
78. Bradley SA, Spring KJ, Beran RG, et al. Role of diabetes in stroke: Recent advances in pathophysiology and clinical management. *Diabetes/ metabolism research and reviews*. 2022;38(2):e3495.DOI: 10.1002/dmrr.3495.
79. Xie XX, Liu P, Wan FY, et al. Blood pressure lowering and stroke events in type 2 diabetes: A network meta-analysis of randomized controlled trials. *International journal of cardiology*. 2016;208:141-6.DOI: 10.1016/j.ijcard.2016.01.197.
80. Lim S, Oh TJ, Dawson J, et al. Diabetes drugs and stroke risk: Intensive versus conventional glucose-lowering strategies, and implications of recent cardiovascular outcome trials. *Diabetes, obesity and metabolism*. 2020;22(1):6-15.DOI: 10.1111/dom.13850.