IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
December 2023 Vol.:29, Issue:1

Occurrence of Ischemic Stroke in Patients with Thrombosis, Cardiovascular Disease and COVID-19

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

I.Mythili[1], SM.Vanmathi[2*], Jayaraman Rajangam[3]

UG Student[1], Assistant Professor, Dept of Pharmacy Practice[2], Principal,
Shri Venkateshwara College of Pharmacy[3], Puducherry- 605102. India.

Submitted: 25 November 2023
Accepted: 30 November 2023
Published: 30 December 2023

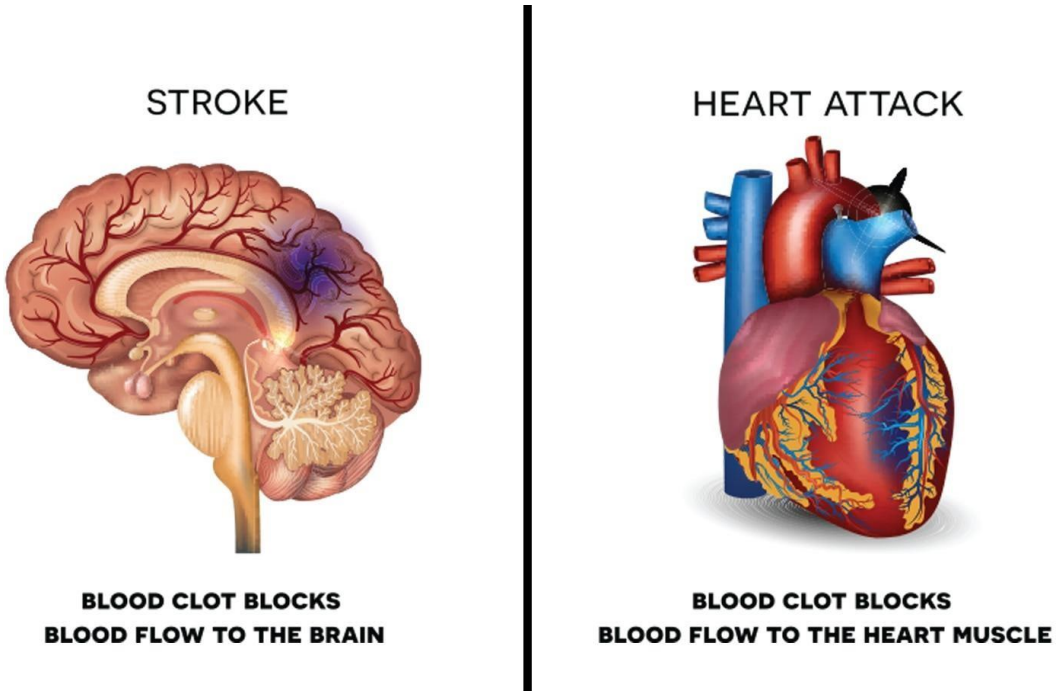
Keywords: ischemic stroke, atherosclerosis, thrombosis, cardiovascular disease (CVD)

ABSTRACT

Stroke is a significant cause of disability worldwide and is considered a disease caused by long-term exposure to lifestyle-related risk factors. An ischemic stroke occurs when there is a blockage or reduction of blood flow to a part of the brain, often due to a blood clot. Thrombosis refers to the formation of a blood clot within a blood vessel, which can lead to various health issues, including ischemic stroke. Risk factors include cigarette smoking, older age, hypertension, dyslipidemia increased amount of risk factors of thrombotic stroke. Cardiovascular disease (CVD) is a broad term that encompasses various conditions affecting the heart and blood vessels. Ischemic stroke and CVD are closely related because they often share common risk factors and mechanisms. Many risk factors for CVD, such as hypertension (high blood pressure), diabetes, smoking, high cholesterol, obesity, and physical inactivity, also contribute to the development of ischemic stroke. These risk factors can lead to the buildup of fatty deposits (atherosclerosis) in blood vessels, including those supplying the brain. When atherosclerosis occurs in the carotid arteries (major blood vessels in the neck), it can increase the risk of both heart disease and ischemic stroke. Stroke risk factors in COVID-19 patients might include pre-existing cardiovascular conditions, advanced age, and other underlying health issues. Among these patients (covid-19, cardiovascular disease, and thrombosis) there is a higher prevalence of ischemic stroke in cardiovascular disease and further, it can be prevented by managing and controlling these risk factors through lifestyle changes (such as a healthy diet, regular exercise, smoking cessation) and, in some cases, medications, can significantly reduce the risk of both cardiovascular disease and ischemic stroke.

INTRODUCTION:

Stroke is usually caused by a blood clot that blocks the blood vessels in the brain and has become a common cause of disability and mortality all over the world over 82% of all incidents are "ischemic strokes"(1). Ischemic stroke with thrombosis as pathology and concern with atherosclerosis. Atherosclerosis may lead to narrowing chronic luminal that obstructs blood flow resulting in angina (2, 3, 4). Acute obstruction of the carotid artery also leads to a stroke, which includes cigarette smoking, older age, hypertension, dyslipidemia increased amount of risk factors of thrombotic stroke(5). Cardiovascular disease risk factors include (unhealthy dietary intake, physical inactivity, dyslipidemia diabetes, high blood pressure, and obesity) (6, 7). COVID-19 also increases the risk of acute ischemic stroke. They are higher frequency of hypertension, diabetes, hyperlipidemia, atrial fibrillation, and congestive heart failure. The patient with COVID-19 who developed acute ischemic stroke had a higher cardiovascular event during hospitalization including cerebral edema, intracerebralhemorrhage, and myocardial infarction. (8)



EPIDEMIOLOGY:

Stroke is ranked as the 2nd leading cause of death worldwide with an annual mortality rateof about "5.5 million". 15 million people suffer stroke worldwide annually of these (5 million

die and5 million are disabled). In 2020, globally the stroke reveals the lifetime risk of stroke has increased by50% over the last 17 years. Now one in 4 people is estimated to have a stroke (9) In 2013, the estimated number of incident ischemic strokes across the globe was 25.7 million stroke survivors and 6.5 million deaths. From 1975-2005 the estimated number of ischemic stroke deaths was 4.85 million (10, 11). In2010, the estimated number of ischemic strokes was 11.6 million. In 2016- 2.7 million death of all strokes about 87% were ischemic strokes, and global ischemic stroke in 2017 was 101.3(91-113.6) per 100,000 population (12). Acute ischemic stroke (AIS) is a well-known complication of COVID-19 infection (COVID-19). Patients with AIS and COVID-19 were significantly more obese (19.1% vs 16.9%) and more likely to be diabetic (46.0% vs 38.6%). Patients with AIS alone had significantly higher rates of smoking (40.8% vs 25.7%) and CAD 25.6% vs 22.65) (13, 14, 15). Stroke is leading to serious long-term disability, reducing mobility in more than half of stroke survivors aged 65 and above. In the US, stroke leads to death in 1 out of 20 deaths. In 2018, 13.7% of all adults (13.7% of all adults (34.2 million people). Cigarette smoking (15.6-male and 12.0-female) (16, 17, 18).

Stroke in India was currently higher than in other Western countries. The first community-based study was carried out in the town of Vellore, south India between 1968 and 1969. The second one was conducted in north India during 1971-1974. This shows a very low prevalence of stroke whichleads to less frequent in India compared to other Western countries. During the 1980s and 1990s, surveys were conducted in various countries (urban and rural) these surveys established prevalence from 1.27 to 2.20 per 1,000 people (19). Stroke is the leading cause of death in India it also determined the mortality rate through an autopsy in 180,162 population in 45 villages of Andhra Pradesh. Stroke causesdeath in 135 very similar to CAD death. Hence, in India, pooled data of all ischemic stroke occurs in 68-80%.

Out of 610 patients with acute stroke of which 110(185 tested covid 19) majorly (72.7%) were men aged 57.5 years and the duration of covid-19 symptoms last for 6 days. Ischemic strokeswere observed in 85.5% of patients. (20)

RISK FACTORS OF THROMBOSIS:

Thrombosis is intravascular (arterial/venous) coagulation of blood resulting in a blood clot that obstructs a vessel (thromboembolism) an acute obstruction of the carotid artery may lead to stroke. The risk factors associated with thrombosis include cigarette smoking, arterial

fibrillation, obesity, diabetes mellitus, etc. Among the most common preventable thrombosis is tobacco cigarette smoking, which majorly leads to overall cardiovascular disease morbidity and mortality (E-cigarettes are the most frequently used tobacco product among youth (5% of middle school students and 20% high school students). The risk factors associated with thrombosis are classified into weak risk factors: (diabetes mellitus, arterial hypertension, and obesity). (21)

Diabetes is associated with a hypercoagulable state and vascular damage, which plays a causal role in venous thromboembolism (VTE), because the association was attenuated after accounting for BMI, some of the association with diabetes mellitus is likely related to a higher prevalence of obesityamong people with diabetes. (22)

Obesity is defined as (BMI=weight \ height) between 30 and 40 obesity can cause increased immobility and is associated with reduced fibrinolytic activity. In addition, obesity is associated with such conditions as congestive heart failure, myocardial infarction, and cholesterol, all of which increase the risk factor of developing thrombosis. (23)

The elderly often have an association with co-morbid conditions, such as surgery and malignancy, which are additional risk factors. The hemostatic system of the elderly has increased levels of fibrinogen prothrombin activation and protein C activation. Lastly, decreased activity of the fibrinolytic system, decreased level of plasminogen activator and increased level of plasminogen inhibitor have been observed in the elderly. (24)

Minor surgery is associated with the release of clotting factors from tissue trauma and venous stasis from post-operative immobilization. (25)

Moderate risk factors like stroke: the level of correlation between thrombosis and stroke ranges from 28-50%. A major ischemic stroke can be associated with prolonged immobilization and confinement that leads to venous stasis and an increased risk of thrombosis deep vein thrombosis DVTand can be prevented from being diluted and released by normal blood flow. (26)

Strong risk factor includes myocardial infarction (MI): myocardial infarction can lead to increased activation of the coagulation system, immobilization, and venous stasis. In addition, myocardial infarction is a reflection of underlying systemic atherothrombotic disease. The incidence of venous thromboembolism is variable across countries and lower in

Eastern countries. (27)

RISK FACTORS OF CARDIOVASCULAR DISEASE:

The risk factor associated with cardiovascular disease includes high blood pressure, diabetes mellitus, and physical inactivity.

High blood pressure is the most important risk factor for ischemic stroke and lowering blood pressure reduces the risk of stroke. When persistently elevated above ranges established by themedical organization, adversely affects patient health (28).

Diabetes mellitus: hyperglycemia may contribute to atherosclerosis via direct mechanism direct adverse effect of elevated glucose levels including endothelial dysfunction, oxidative stress, etc. females with a prior history of gestational diabetes are at increased risk of development of type 2 diabetes mellitus. Many risk factors for CVD are also risk factors of gestational diabetes example: increases body fat, increase age, hypertension, and decreased HDL-C.

Physical inactivity: the increased risk of heart and circulatory disease are being inactive can lead to fatty material building in arteries that lead to damage and clogging. Physical inactivity increases the risk of cardiovascular disease. Only 50% of adults get sufficient physical inactivity to reduce the risk of many chronic diseases such as CVD. Worldwide, approximately 3.9 million premature deaths annually are prevented with adequate physical activity (29).

PREVALENCE OF CVD:

Stroke is a strong risk factor for recurrent cardiovascular disease (CVD) events. For a patient with extremely high-risk factor post-ischemic stroke patients who suffered recurrent cardiovascular incidents were more frequently observed to have depression, insomnia, and abnormal, heart rhythm. Patients who have undergone ischemic stroke are at high risk of cardiovascular disease (CVD), according to World Health Organization (WHO) experts nearly 80%of repeated CVD events could be avoided if main risk factors like arterial hypertension, arterial fibrillation, diabetes, insomnia, smoking, alcohol abuse factor were removed. The pathogenesis of ischemic stroke in COVID-19, like other arterial thrombosis seen in diseases such as peripheral arterial thrombosis and myocardial infarction, is likely

multifactorial, stemming from inflammation and coagulopathy. Cardio embolism about 20% of hospitalized covid 19 patient suffers cardiac injury, which can lead to arrhythmia and acts as a direct source of cerebral embolic. recent evidence suggests that covid 19 can also affect the cardiovascular and cerebrovascular system. In that study they investigated 41 patients with covid 19 in Wuhan, and observed arterial hypertension and cardiovascular disease in 6(15%) patients. some patients with covid 19 have reported having a stroke due to cardio embolism (30).

THROMBOSED PULMONARY IN COVID 19 LEADS TO STROKE:

Stroke is a major burden on patients, caregivers, the healthcare system, and society. At the beginning of this century, approximately 1.1 million inhabitants of Europe suffered a stroke each year.These numbers are expected to increase by 2025 to 1.5 million owing to the aging population and the persistence of risk factors. The pathogenesis of ischemic stroke in coronavirus disease 2019 (covid 19), is similar to other arterial thromboses seen in this disease, such as peripheral likely multifactorial stemming from inflammation and coagulopathy (31).

STROKE IN COVID 19 PATIENT:

During the pandemic, independent institutions have observed a decreased volume of stroke emergencies across the globe. A systematic review conducted in May 2020, has reported that 48.8%of neurological involvement in covid 19 patients were cerebrovascular incidents, which consisted of 87.5%ischemic stroke.

The majority of ischemic stroke subtypes were large vessel occlusion, which consisted of 77% within a total pooled sample of 35 ischemic stroke cases. The association between cerebrovascular disease and severe covid 19 was borderline significant. This is a stark contrast with the findings, who had reported an increase in an odd association between CVD and severe covid 19 infection and no statistical significance in the association between CVD and mortality in severe covid 19 patients (32).

GLOBAL CORONA VIRUS DISEASE 2019(COVID19) PANDEMIC AND STROKE PREVALENCE:

On 11 March 2020, the World Health Organization (WHO) declared covid 19 a global

pandemic. The impact of the COVID-19 pandemic on healthcare systems around the world. The COVID-19 pandemic is associated with neurological symptoms and complications including stroke.

Some COVID-19 patient develops stroke, seizure, confusion, and brain inflammation. A case report described a Chinese patient with covid 19 with left hemiparesis due to acute cerebral infraction and large blood vessel occlusion as well as a patient with covid 19 with massive intracerebral hemorrhage(ICH) without prior history of atrial hypertension.

Outcomes of the patient who suffers from stroke as a complication of covid 19. Although the incidence of stroke in hospitalized covid 19 patients was low at 1.74%, the mortality rate of patients who suffered from stroke as a complication of covid 19 patients, stroke was associated with older age, comorbidities, and severe illness. Pathophysiology and prognosis of stroke in covid 19, improving theeffectiveness of care (33).

COMORBIDITY IN CARDIOVASCULAR DISEASE:

A comorbidity relationship occurs whenever two or more diseases are present in the same individual more often than by chance alone. Cardiovascular disease is leading cause of human mortality worldwide. One reason behind this lethality lies in the fact that often-cardiovascular illness develops into systemic failure due to multiple connections to organismal metabolism. This in turn is associated with comorbidities and multi-morbidity.

COMORBIDITIES OF COVID 19:

Ischemic stroke risk did not vary by race, in contrast to the association between older age and death from covid 19, ischemic stroke risk was the highest among middle-aged adults after adjusting for comorbidities and illness severity, suggesting a potential mechanism for ischemic strokein covid 19 independent of age-related atherosclerotic pathways.

COMORBIDITIES OF THROMBOSIS:

Comorbidity is prevalent among stroke patients, affecting post-stroke survival. It remains unknown whether comorbidity impacts post-stroke mortality beyond the combined individual effects of stroke and comorbidity. During 1st year of follow-up, initially 30 day period, interaction with comorbidity resulted in increased post-stroke mortality across all comorbidity levels, all individual comorbidities, all age groups, and among ischemic stroke

patients. Among adults below, age 60 years. The interaction was seen for up to 5 years, because of interaction, 30 days post-stroke were increased at an excess of 47, 81 and 180 deaths per month for every 1000 patients with low moderate and high comorbidity, respectively. This excess mortality because of interaction represented 23%, 34%, and 51% of the total rate among stroke patients with low moderate and high comorbidity. This excess 30 days of mortality because of interaction represented 33%, 44% of the total mortality rate among ischemic stroke patients. The interaction contrast was least pronounced among stroke patients with cardiovascular comorbidity.

DISCUSSION:

Stroke is ranked as the 2nd leading cause of death worldwide with an annual mortality rateof about "5.5 million". 15 million people suffer a stroke worldwide annually of these (5 million die and 5 million are disabled). In 2020, globally the stroke reveals the lifetime risk of developing stroke has increased by 50% over the last 17 years. Now one in 4 people is estimated to have a stroke. Thrombosis is intravascular (arterial/venous) coagulation of blood resulting in a blood clot that obstructs a vessel (thromboembolism) an acute obstruction of the carotid artery may lead to stroke. Cigarette smoking, arterial fibrillation, obesity, diabetes mellitus, etc. are all risk factors. Stroke is a strong risk factor for recurrent cardiovascular disease (CVD) events. For a patient with extremely high-risk factor post-ischemic stroke patients who suffered recurrent cardiovascular incidents were more frequently observed to have depression, insomnia, and abnormal, heart rhythm. At the beginningof this century, approximately 1.1 million inhabitants of Europe suffered a stroke each year.

Comorbidity is common in stroke patients, reducing post-stroke survival. In contrast to the link between older age and death from covid 19, the risk of ischemic stroke did not differ by race. After controlling for comorbidities and illness severity, ischemic strokes were most common in middle-aged adults.

CONCLUSION:

From the above risk factors and prevalence, cardiovascular disease (CVD) patients, particularly those with certain risk factors, have a higher rate of ischemic stroke. Ischemic stroke is a type of stroke that occurs when there is a blockage or clot in a blood vessel supplying blood to the brain, leading to a lack of blood flow and oxygen. This can result in

brain damage and other serious complications it can managing and controlling these risk factors through lifestyle changes (such as a healthy diet, regular exercise, and smoking cessation) and, in some cases, medications, can significantly reduce the risk of both cardiovascular disease and ischemic stroke. Immediate medical intervention to restore blood flow to the brain, such as thrombolytic therapy or mechanical thrombectomy, may be crucial to minimize brain damage and optimize the chances of recovery. Concurrently, managing the underlying cardiovascular condition becomes equally paramount, involving tailored treatment strategies to address factors such as hypertension, atherosclerosis, and arrhythmias. Furthermore, a robust long-term management plan should encompass lifestyle modifications, medication adherence, and regular follow-up appointments. Collaborative efforts among neurologists, cardiologists, rehabilitation specialists, and other healthcare providers are essential to address both the acute and chronic aspects of this complex medical scenario. Science. Individuals with CVD need to work closely with their healthcare providers to minimize theserisks and optimize their overall health.

REFERENCES:

1. Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significance beyond thrombolysis. Pathophysiology. 2010 Jun 1; 17(3):197-218.
2. Zhang H, Liu J, Liu Y, Su C, Fan G, Lu W, Feng L. Hypertonic saline improves brain edema resulting from traumatic brain injury by suppressing the NF-κB/IL-1β signaling pathway and AQP4. Experimental and therapeutic medicine. 2020 Nov 1; 20(5):1-.
3. Adams Jr HP, Biller J. Classification of subtypes of ischemic stroke: history of the trial of org 10 172 in acute stroke treatment classification. Stroke. 2015 May; 46(5):e114-7.
4. Nam KW, Kwon HM, Jeong HY, Park JH, Kim SH, Jeong SM. High neutrophil-to-lymphocyte ratios predict intracranial atherosclerosis in a healthy population. Atherosclerosis. 2018 Feb 1; 269:117-21.
5. Tremblay MS, Bryan SN, Pérez CE, Ardern CI, Katzmarzyk PT. Physical activity and immigrant status: evidence from the Canadian Community Health Survey. Canadian journal of public health. 2006 Jul; 97:277-82.
6. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circulation research. 2016 Apr 29; 118(9):1340-7.
7. Marto JP, Strambo D, Livia F, Michel P. Drugs associated with ischemic stroke: a review for clinicians. Stroke. 2021 Oct; 52(10):e646-59.
8. Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, Abd-Allah F, Abdelalim A, Abraha HN, Abu-Rmeileh NM, Adebayo OM. Global, regional, and national burden of stroke, 1990–2016: asystematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2019 May 1; 18(5):439-58.
9. Ornello R, Degan D, Tiseo C, Di Carmine C, Perciballi L, Pistoia F, Carolei A, Sacco S. Distribution and temporal trends from 1993 to 2015 of ischemic stroke subtypes: a systematic review and meta-analysis. Stroke. 2018 Apr; 49(4):814-9.
10. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson LM, Truelsen T, O'Donnell M. Global and regional burden of first-ever ischemic and hemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. The Lancet Global Health. 2013 Nov 1; 1(5):e259-81.
11. IHME (Institute for Health Metrics and Evaluation). GBD compares data visualization. IHME. 2016.
12. Kariyanna PT, Chandra Kumar HP, Jayarangaiah A, Khan A, Vulkanov V, Ashamalla M, Salifu MO,

McFarlane SI. Apical takotsubo cardiomyopathy in a COVID-19 patient presenting with stroke: a case report and pathophysiologic insights. American journal of medical case reports. 2020; 8(10):350.
13. Majeed H, Gangu K, Sagheer S, Garg I, Khan U, Shuja H, Bobba A, Chaurasia P, Shekhar R, Avula SR, Sheikh AB. COVID-19 and NSTEMI Outcomes among Hospitalized Patients in the United States and Racial Disparities in Mortality: Insight from National Inpatient Sample Database. Vaccines.2022 Nov 26; 10(12):2024.
14. Hodge JG, Gostin LO. Revamping the US Federal Common Rule: Modernizing human participant research regulations. JAMA. 2017 Apr 18; 317(15):1521-2.
15. Centers for Disease Control and Prevention. Smoking & tobacco use. Fast facts and fact sheets. Fast Facts, Fact Sheets| Smoking, and Tobaco Use| CDC. Available online: https://www. cdc. go/tobacco/data statistics/factsheets/index. Htm (accessed on 1 January 2022). 2020.
16. Kids T. Quick facts on the risks of e-cigarettes for kids, teens, and young adults.
17. Abraham J, Rao PS, Inbaraj SG, Shetty G, Jose CJ. An epidemiological study of hemiplegia due to stroke in South India. Stroke. 1970 Nov; 1(6):477-81.
18. Bansal BC, Prakash C, Jain AL, Brahmanandam KR. Cerebrovascular disease in young individuals below the age of 40 years. Neurology India. 1973 Mar 1; 21(1):11-8.
19. Joshi R, Cardona M, Iyengar S, Sukumar A, Raju CR, Raju KR, Raju K, Reddy KS, Lopez A, Neal B. Chronic diseases are now a leading cause of death in rural India mortality data from the Andhra Pradesh Rural Health Initiative. International journal of epidemiology. 2006 Dec 1; 35(6):1522-9.
20. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Sacco C, Bertuzzi A, Sandri MT. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thrombosis research. 2020 Jul 1; 191:9-14.
21. Wang TW, Neff LJ, Park-Lee E, Ren C, Cullen KA, King BA. E-cigarette use among middle and high school students United States, 2020. Morbidity and Mortality Weekly Report. 2020 Sep 9; 69(37):1310.
22. Aguiar de Sousa D, von Martial R, Abilleira S, Gattringer T, Kobayashi A, Gallofré M, Fazekas F, Szikora I, Feigin V, Caso V, Fischer U. Access to and delivery of acute ischemic stroke treatments: a survey of national scientific societies and stroke experts in 44 European countries. European stroke journal. 2019 Mar; 4(1):13-28.
23. Caprini JA, Arcelus JI, Hasty JH, Tamhane AC, Fabrega F. Clinical assessment of venous thromboembolic risk in surgical patients. In Seminars in thrombosis and hemostasis 1991 Jan 1 (Vol. 17, pp. 304-312).
24. Hirsh J, Genton E, Hull R. A practical approach to the prophylaxis of venous thrombosis. In Venous thromboembolism 1981 (Vol. 1, pp. 108-121). Grune & Stratton New York.
25. Brenner DW, Fogle MA, Schellhammer PF. Venous thromboembolism. The Journal of Urology. 1989 Dec 1; 142(6):1403-11.
26. Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. Jama. 1995 Jul 26; 274(4):335-7.
27. Nicolaides AN, Kakkar VV, Renney JT, Kidner PH, Hutchinson DC, Clarke MB. Myocardial infarction and deep-vein thrombosis. Br Med J. 1971 Feb 20; 1(5746):432-4.
28. Yamamoto H, Bogousslavsky J. Mechanisms of second and further strokes. Journal of Neurology, Neurosurgery & Psychiatry. 1998 Jun 1; 64(6):771-6.
29. Tripathy D, Merovci A, Basu R, Abdul-Ghani M, DeFronzo RA. Mild physiologic hyperglycemia induces hepatic insulin resistance in healthy normal glucose-tolerant participants. The Journal of Clinical Endocrinology & Metabolism. 2019 Jul; 104(7):2842-50.
30. Singh R, Pattisapu A, Emery MS. US Physical Activity Guidelines: Current state, impact and future directions. Trends in cardiovascular medicine. 2020 Oct 1; 30(7):407-12.
31. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, Naghavi M, Mensah GA, Murray CJ. Demographic and epidemiologic drivers of global cardiovascular mortality. New England Journal of Medicine. 2015 Apr 2; 372(14):1333-41.
32. Skajaa N, Adelborg K, Horváth-Puhó E, Rothman KJ, Henderson VW, Thygesen LC, Sørensen HT. Risks of stroke recurrence and mortality after first and recurrent strokes in Denmark: a nationwide registry study. Neurology. 2022 Jan 25; 98(4):e329-42.
33. Siegler JE, Heslin ME, Thau L, Smith A, Jovin TG. Falling stroke rates during the COVID-19 pandemic at a comprehensive stroke center. Journal of Stroke and Cerebrovascular Diseases. 2020 Aug 1; 29(8):104953.
34. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T.

Neurological associations of COVID-19. The Lancet Neurology. 2020 Sep 1; 19(9):767.