DOI: https://doi.org/10.61841/w0n2j027 Publication URL: https://nnpub.org/index.php/MHS/article/view/2240

THE STUDY OF RISK FACTOR AND STRATEGIES FOR PREVENTION OF RECURRENT ISCHEMIC STROKE :A COMPREHENSIVE SYSTEMATIC REVIEW

[*1]Ibnu Ibni Rizal, [2]Ghiffany Octaviantie

*[*1]Bekasi Regency Regional General Hospital, Indonesia*
[2]Faculty of Medicine, Muhammadiyah University of Jakarta, Indonesia

Correspodence Author:
ibnuibniryzal@gmail.com

ABSTRACT

Background: *Studies show that the majority of strokes are caused by modifiable risk factors, such as high-fat diets, sleep apnea, diabetes, heart disorders, and other diseases. Recurrence rates are higher in sub-Saharan Africa (SSA), where strokes occur in the fourth or fifth decades of life. To reduce the risk of stroke recurrence and death, individuals who have survived their first stroke must undergo regular medical follow-up. Understanding the risk factors for stroke recurrence can help create plans and treatments to lessen the burden of strokes. Regular medical follow-up and understanding these risk factors can help create effective treatments and plans to reduce stroke recurrence.*

Methods: *This systematic review focused on full-text English literature published between 2014 and 2024, adhering to PRISMA 2020 principles. Without a DOI, editorials and review papers that were published in the same journal as the submission were not accepted. ScienceDirect, PubMed, and SagePub were among the many web resources used to compile the literature.*

Result: *Using reliable resources including Science Direct, SagePub, and PubMed, the study examined over 7,000 publications. Following the determination that seven publications warranted a further inquiry, a more thorough examination of the full corpus was conducted.*

Conclusion: *Risk factors such as hypertension, alcohol consumption, diabetes, female gender, non-adherence to treatment, and cardiac causes contribute to high stroke recurrence rates in sub-Saharan Africa. Treatment effectiveness varies among ethnic groups, with DAPT being effective in patients with ICAD. Statin-based therapies reduce recurrent stroke risk but increase hemorrhagic stroke risk. Vitamin D plays a crucial role in brain development.*

Keyword: *Stroke, recurrent, SSA, DAPT, Vitamin D*

INTRODUCTION

A stroke is characterized as a neurological deficit related to a vascular etiology that results from an immediate focal lesion of the central nervous system, extending to the brain, retina, or spinal cord.[1] According to epidemiological data, strokes are extremely serious and frequent events that account for the second-largest cause of mortality worldwide and the third-largest source of disability. In all, roughly 100 million and 12 million stroke incidents were reported globally in 2019—the total number of prevalent and incident cases. Over 6.5 million fatalities in 2019 were directly related to strokes.[2] As the second most frequent disease globally in 2019, stroke continued to be a major cause of mortality.[3] The majority of strokes are caused by modifiable risk factors, according to the majority of the literature. These include high-fat diets, sleep apnea, diabetes, heart disorders, sickle cell disease, oral contraceptive use, migraines, smoking, migraines, hypertension, dyslipidemia, diabetes, and excessive exercise.[4,5] A worldwide meta-analysis predicted that 11% of people may experience another stroke within a year after their initial one and 26% within five. Antithrombotic, statin, and antihypertensive medications, for example, can lower the risk of secondary vascular events by 20% to 30%, hence preventing secondary strokes.[6]

According to recent studies, approximately 30% of strokes are repeated episodes, and these strokes have a higher chance of leaving a victim disabled or dead.[7] Frequently occurring strokes are linked to not only early death but also substantial social and financial consequences, as well as cognitive and physical impairment. Patients with lacunar infarcts, in particular, have a 4–12 times higher diagnosis rate than the general population for dementia. Subcortical dementia is caused by recurrent lacunar strokes, and the most significant predictor of mortality is a cardioembolic stroke.[3] Individuals who survive their first stroke are at high risk of having another one. A Stoke recurrence is defined as a new focal neurological deficit of vascular origin lasting more than twenty-four hours, at least twenty-eight days following the incident event, or as an abrupt functional decline in neurological status with a drop of four points or more on the National Institute of Health Stroke Scale (NIHSS).[8] Mohan et al. performed a meta-analysis based on 13 studies published before to 2009 with 9115 stroke survivors. The results indicate a progressive increase in the pooled cumulative risk of stroke recurrence, from 3.1% at 30 days to 39.2% at 10 years after the initial stroke.[9]

Most people are aware of the major and predicted risk factors for stroke.[4,10] On the other hand, less is known about the risk factors for stroke recurrence especially in some areas.[11] According to studies, sub-Saharan Africa (SSA) has higher stroke burden indices than the rest of the globe.[12,13] Estimates of up to 316 cases per 100,000 annually, 1,460 cases per 100,000 annually, and a 3-year fatality rate above 80% have been made in SSA within the last ten years.[12,14] Most of these strokes happen in the fourth or fifth decades of life, which has a significant negative impact on the socioeconomic output of people in SSA and has serious ramifications for families and society.[3] A subsequent, more current meta-analysis by Lin and colleagues, which examined 37 research with over a million participants and was published between 2009 and 2019, provided strong confirmation of these data.[15] Recurrence of a stroke also raises the chance of death from stroke and all other cardiovascular causes. In light of the aforementioned, it is crucial in these situations to avoid a stroke from happening again. Therefore, to lower the risk of stroke recurrence and death, people who have survived a first stroke must undergo regular medical follow-up. Both new and ancient blood indicators have made this possible.[16] Knowing the pertinent risk factors for stroke recurrence in a given person may be useful in creating plans and treatments to lessen this burden. The purpose of this systematic literature review was to identify stroke recurrence rates and risk variables for recurrent strokes that were discovered in studies conducted over the previous ten years.

METHODS

Protocol

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines were scrupulously followed by the work's author. This was done to make sure the study complied with all rules. The method of choice was carefully created to guarantee the precision and coherence of the research outcomes.

CRITERIA FOR ELIGIBILITY

This study offers a thorough analysis of research conducted in the last ten years on risk factors and preventive measures for recurrent ischemic stroke. Through in-depth data analysis, this project aims to explain and enhance patient care procedures. This thesis' main goal is to highlight the importance of important topics that may be found in a range of literary works.

To guarantee the accuracy of the data used in this study, stringent inclusion and exclusion criteria were implemented. A piece cannot be considered for inclusion unless it was published in English between 2014 and 2024. Published reviews, editorials, submissions without a DOI, and duplicate journal entries are some of the exclusion criteria..

SEARCH STRATEGY

The study's keywords include "ischemic stroke, recurrent stroke, recurrent, prevention, strategies, risk factor". For this research, the following Boolean MeSH keywords were entered into the databases: (((“Ischemic Stroke”[MeSH Terms]

OR “Ischemic Stroke “[All Fields] AND “Recurrent”[All Fields]) OR (“Recurrent Stroke”[MeSH Terms] OR “Recurrent Stroke”[All Fields] AND “prevention”[All Fields]) AND (“Ischemic Stroke”[MeSH Terms] OR “Recurrent Stroke”[All Fields] OR “prevention”[All Fields] OR “strategies”[MeSH Subheading] OR “risk factor”[All Fields] OR “recurrent”[All Fields])))).

DATA RETRIEVAL

Before beginning this lengthy examination, the writers carefully read the title and abstract of each article to ascertain its significance. Only studies that satisfied the inclusion criteria and supported the article's objectives were given more weight. A series of searches led to a conclusive result: a recurrent pattern. The only language in which full-text entries were accepted was English. The most stringent screening process resulted in content that met all predefined inclusion criteria and had a direct bearing on the subject matter of the study. Research that didn't follow these patterns were usually ignored, and their findings weren't given much weight. Numerous pieces of information were found and examined during the assessment, including factors, titles, authors, dates of publication, locations, and study methodologies..

QUALITY ASSESSMENT AND DATA SYNTHESIS

The research referenced in the titles and abstracts of every article was assessed independently by the writers to determine which articles require additional investigation. The following step involved going over each document that was pre-qualified for review inclusion in advance. The evaluation findings serve as a guide for selecting the review papers. By speeding up the selection of publications for additional investigation, this criterion allowed for a more comprehensive evaluation of previous work and the circumstances that qualified it for review.

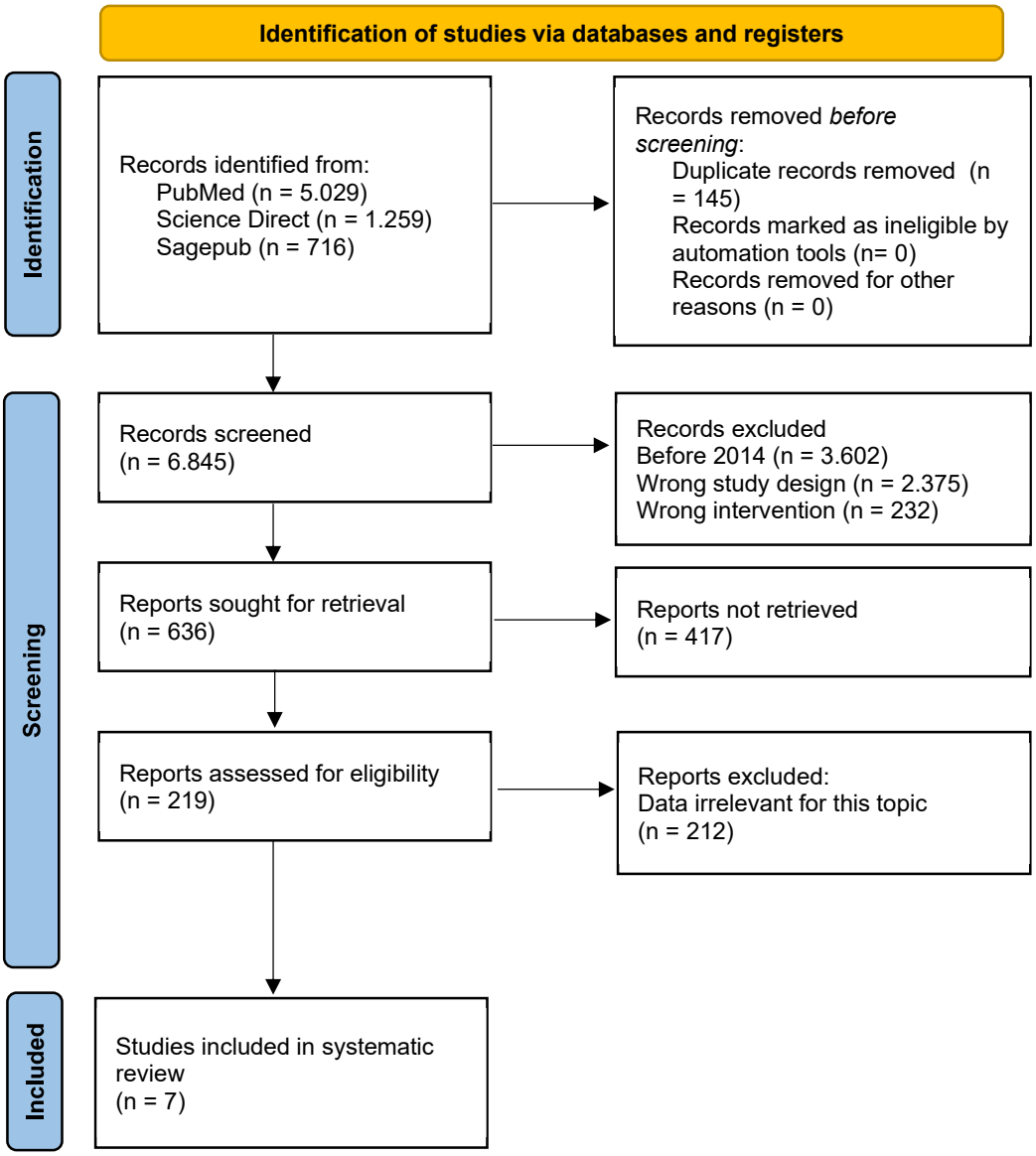

Figure 1. Article search flow chart

RESULT

Initially, our research team gathered nearly three thousand publications from reputable databases such as Science Direct, PubMed, and SagePub. Seven papers were identified through a thorough three-tier screening process as being immediately relevant to our ongoing systematic investigation.. Subsequently, certain areas were chosen for further investigation and a detailed examination of the complete manuscript. For simplicity of viewing, Table 1 provides a summary of the content that was evaluated for this analysis.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Kolmos et al.[17] (2021)	Denmark	Systematic Review	26 studies	The frequency of recurrent strokes varied from 5.7% to 51.3%. With recurrent stroke similar to the index stroke subtype, recurrent stroke was most common in large artery atherosclerosis (LAA) and cardioembolic (CE) stroke. We identified another stroke subtype that recurs more frequently and had a lower recurrence rate than small vessel occlusion (SVO) stroke. Recurrence rates of strokes with a summary proportion of 0.12 and 0.14 in research utilizing TOAST-like criteria, respectively, were found in studies employing TOAST criteria, according to a meta-analysis. There were four independent risk variables for recurrence: high stroke severity, atrial fibrillation before a transient ischemic event, diabetes mellitus, and hypertension.
Shah et al.[18] (2021)	USA	Narrative Review	-	The associated stroke risk is reduced by single-antiplatelet therapy (SAPT) with aspirin, aspirin/dipyridamole, or clopidogrel. Dual-antiplatelet therapy (DAPT) with aspirin and clopidogrel or ticagrelor is more effective than SAPT in patients with minor acute non-cardioembolic ischaemic stroke or high-risk TIA. Prolonged use of DAPT is associated with a higher risk of hemorrhage without stroke recurrence reduction.
Grory et al.[19] (2021)	USA	Review	-	A study revealing a high risk of recurrence in patients with Intracranial atherosclerotic disease (ICAD), a stroke subtype, found a 19% risk of recurrent ischemic stroke at 2 years, with 75% occurring in the stenotic artery. Silent infarcts were also found to be

				significantly higher, with 25% of recently symptomatic ICAD patients experiencing a new infarct at 6-8 weeks.
Lee et al.[20] (2022)	Taiwan	RCT	20.163 patients	The study analyzed 11 randomized clinical trials involving 20.163 patients with stroke. Results showed that more intensive LDL-C-lowering statin-based therapies were associated with a reduced risk of recurrent stroke compared to less intensive therapies. However, these therapies also increased the risk of hemorrhagic stroke. The evidence suggests that more intensive statins may reduce the risk of stroke in patients with atherosclerosis, but not in those without atherosclerosis.
Bangad et al.[21] (2013)	USA	Review	-	Stroke prevention is crucial in reducing the risk of recurrent ischemic stroke, a major public health concern. Secondary treatments, including medical and surgical interventions, aim to reduce the risk of recurrent stroke. These strategies consider the mechanism of the first stroke and related vascular risk factors. Providers, healthcare systems, and insurers must consider treatment availability, cost, patient burden, adherence methods, and interventions targeting lifestyle risk factors.
Vergatti et al.[16] (2017)	Italy	Meta Analysis	4 studies	In order to compare the highest and lowest values, a random-effects model was employed to assess the pooled estimated risk (and 95% CI) of stroke recurrence. A non-linear correlation was found in the dose-response investigation. This study found that 25(OH)D levels at the time of the first stroke of ≥9.3 ng/mL, as opposed to ≤8.5 ng/mL, were associated with a lower risk of stroke recurrence. Higher 25(OH)D levels at the time of the first stroke significantly reduce the risk of stroke recurrence, but the pooled analysis shows that

				there is substantial variability among the studies.
Mbalinda et al.[3] (2024)	Multicenter	Systematic Review	6 studies	The rate of stroke recurrence in Sub-Saharan Africa (SSA) ranged from 9.4% to 25%. The bulk of the studies, which were conducted in Western Africa, showed that stroke recurrence rates, which can range from 2% to 25%, are noteworthy in sub-Saharan Africa. Stroke recurrence is still mostly caused by known risk factors for stroke, such as high blood pressure and chronic alcohol consumption. The study found that persons with recurrent strokes had a higher death rate—between 20.5 and 23%—than those with primary strokes.

A study by Kolmos et al. has reported risk factors associated with stroke recurrence, including a history of hypertension, diabetes mellitus, atrial fibrillation, angina, ischemic heart disease, and cardiomyopathy. Lifestyle factors, prior IS or TIA, increased stroke severity, a high NIHSS score, and a modified Rankin Scale at discharge were also identified as independent predictors. A meta-analysis of proportions comparing stroke recurrence reported in each study found high heterogeneity and a sub-analysis of recurrent stroke by subtype.[17]

According to Shah et al.'s review, SAPT is linked to a lower risk of recurrent ischemic stroke in patients who have had a transient ischemic attack or non-cardioembolic ischemic stroke. For high-risk TIA or small acute noncardioembolic ischemic stroke, dual-antiplatelet treatment (DAPT) including aspirin and clopidogrel or ticagrelor is more beneficial than salvage autopsy. For secondary stroke prevention in non-cardioembolic ischemic stroke or transient ischemic attack (TIA), SAPT is advised, whereas DAPT with aspirin and clopidogrel or ticagrelor is advised.[18]

Grory's study revealed that Intracranial atherosclerotic disease (ICAD) is the most common cause of ischemic stroke worldwide, causing up to 50% of strokes in Asia and disproportionately affecting minorities in the United States. ICAD is the stroke subtype with a high risk of recurrence, with silent infarcts being significantly higher.[19]

The study by Lee et al. found that more intensive LDL-C-lowering statin-based therapies were associated with a reduced risk of MACE, recurrent ischemic stroke, and myocardial infarction. The benefit was not statistically different among the LDL-C-lowering strategies, and the risk was not significantly different among the LDL-C-lowering strategies.[20]

The enormous health burden of ischemic stroke, is a significant public health concern, as highlighted by Bangad's study. Reducing the chance of another stroke is the goal of secondary stroke prevention techniques, which include medication and surgical procedures. These approaches take into account the cause of the initial stroke, cardiovascular risk factors, accessibility to therapy, expense, patient burden, and lifestyle modifications.[21]

Vergatti et al. reported that ischemic and hemorrhagic strokes, with higher 25(OH)D levels at the first stroke event associated with a significantly lower risk of stroke recurrence. The study found a non-linear association between 25(OH)D levels and the risk of recurrent stroke, with 25(OH)D levels ≥ 9.3 ng/mL associated with a significantly lower risk. The study also found significant heterogeneity among studies, indicating a potential publication bias.[16]

Mbalinda's studies reveal that recurrent strokes are associated with various risk factors in SSA. Hypertension, alcohol consumption, female sex, non-compliance with therapy, right-handedness, congestive heart disease, gout, facial palsy, dysarthria, and dyslipidemia are the most common vascular risk factors for recurrent strokes. Other risk factors include female sex, non-compliance with therapy, right-handedness, congestive heart disease, gout, and older age.[3]

DISCUSSION

The recurrence rate of stroke that occurs again has not changed in the last two decades despite new and more effective acute treatments being developed.[17] The known risk factors are the primary factors linked to stroke recurrence, and these

factors are prevalent in sub-Saharan Africa. Recurrent strokes have a higher death rate than original strokes. The following are independent risk factors for recurrent stroke: female gender, diabetes mellitus, hypertension, alcohol consumption in the past, non-adherence to post-stroke treatment, and cardiac causes.[3] The highest recurrence rate was observed in LAA and CE strokes, often following an LAA-LAA or CE-CE recurrence pattern. SVO stroke had a lower recurrence rate of clinical stroke compared to other TOAST subtypes, and SVO stroke was often followed by another stroke subtype.[17] Smoking, HT, DM, AF, prior cerebrovascular events, and increased severity of stroke are independent risk factors of recurrent stroke.[4] In sub-Saharan Africa, hypertension is a significant modifiable risk factor for stroke burden and recurrent strokes. Recurrence of stroke can be decreased with medication adherence and consistent attendance at follow-up clinics.[22] On the other hand, it has been noted that a lack of awareness among stroke survivors causes delays in prompting medical attention and medication compliance. Three studies have found a correlation between alcohol consumption and the risk of stroke recurrence among stroke survivors.[23] Diabetes mellitus has also been associated with recurrent stroke, consistent with previous studies.[3] The small progress within non-AF secondary prevention and the increasing age and load of cardiovascular risk factors in the general population may balance out the effect of advances in stroke diagnostics and acute interventions on the stroke recurrence rate.[17] The risk of stroke recurrence is high in ICAD, a stroke subtype with a high risk. The WASID study found a 19% risk of recurrent ischemic stroke at 2 years, with 75% occurring in the stenotic artery. Clinical features, including women and the early period after index events, are associated with greater risk.[19] Imaging biomarkers, multiple infarcts, and border zone patterns are associated with higher risk.[24] The study reveals that poor cholesterol control, low-density lipoprotein, elevated blood pressure, and inadequate physical activity are associated with greater stroke and major cardiovascular event recurrence, suggesting the need for early post-stroke management strategies.[19]

Antiplatelet therapy is an important treatment for stroke prevention, especially in Asian populations. However, the effectiveness of this therapy varies among different ethnic groups. It is important to determine the optimal dosage, combination, and duration of antiplatelet medications for patients with multiple risk factors, high BMI, and genetic mutations such as the CYP2C19 loss-of-function gene.[18] Individuals who carry the CYP2C19 loss-of-function gene are at greater risk of stroke. Therefore, further research is needed to evaluate the use of CYP2C19 gene testing-based antiplatelet therapy for stroke prevention.[25] For patients with aortic arch and intracranial atherosclerotic disease, ticagrelor may be more effective than aspirin. However, it is important to consider the patient's bleeding risk before prescribing this medication. Studies have shown that increasing the dose of aspirin or switching to another antiplatelet agent after recurrent TIA or AIS is not effective.[18,26] DAPT (dual antiplatelet therapy) is effective in preventing stroke in patients with intracranial arterial disease (ICAD).[19] The SAMMPRIS trial found that DAPT for 90 days was superior to aspirin in preventing the recurrence of stroke in the initial period after an index event. The THALES trial also found that DAPT reduces the risk of recurrent stroke in patients with ICAD.[26] However, the CHANCE trial did not find a difference between aspirin and clopidogrel versus aspirin alone in stroke recurrence at 90 days.[27] Studies have not found an increase in hemorrhagic complications with DAPT in ICAD patients. Researchers are also investigating other drugs, such as cilostazol and oral factor XIa inhibitors, for secondary stroke prevention. However, a recent study failed to show a benefit for these agents.[28] New lipid-lowering agents like bempedoic acid, monoclonal antibodies, and RNA knockdown strategies are also being studied. However, before widespread adoption, the cost, side effects, and effectiveness of these drugs must be evaluated.[21]

According to a recent analysis of 11 randomized clinical trials involving over 20,000 individuals with a history of stroke, more intensive LDL-C-lowering statin-based therapies were found to be linked to a 12% lower risk of recurrent stroke and a 17% reduced risk of MACE. However, there was also a 46% increased risk of hemorrhagic stroke and a higher risk for new-onset diabetes associated with these therapies.[20] The antithrombotic properties of statins may be the cause of the increased risk of hemorrhagic stroke, rather than LDL-C levels or the extent of LDL-C-lowering therapies.[29] The effectiveness of statin-based therapies in reducing LDL-C levels varies depending on the cause of the stroke, and there are concerns that this approach may not benefit all patients with ischemic stroke.[20] The recently issued 2021 AHA/American Stroke Association guideline for recurrent stroke prevention recommends atorvastatin, 80 mg daily, for patients with non-cardioembolic ischemic stroke and an LDL-C level greater than 100 mg/dL to reduce the risk of recurrent stroke.[30] However, high-intensity statins should only be used when there is evidence of atherosclerosis. While it may be reasonable to lower LDL-C levels below 70 mg/dL with statin-based therapies for patients with ischemic stroke and evidence of atherosclerosis, the lowest level beyond which LDL-C should not be lowered is not yet clear based on current evidence.[20]

The neuroprotective effect of vitamin D against age-related brain degeneration underscores the critical role that the vitamin D system plays in brain development, function, and maintenance. The risk of a subsequent stroke in patients who have had their first hemorrhagic or ischemic event is positively correlated with 25(OH)D levels, according to a recent meta-analysis..[16] Vitamin D is responsible for regulating calcium-phosphate homeostasis, renin secretion, insulin sensitivity, and vascular calcifications. Furthermore, low 25(OH)D levels are associated with dyslipidemia, atherosclerosis, and atherosclerosis plaque formation. Vitamin D also plays a role in modulating the immune response and cytokine biosynthesis, which can help reduce inflammatory and autoimmunity responses.[16] The cardiovascular system now

recognizes vitamin D as a non-canonical target, as it regulates calcium cell influx, endothelial cell survival, and inflammatory response.[31] The fact that vitamin D deficiency is thought to be a substantial risk factor for stroke and other chronic degenerative and cardiometabolic disorders is crucial to remember. A non-linear relationship between 25(OH)D levels and stroke recurrence was discovered in a recent dose-response analysis, with low levels of 25(OH)D being negatively correlated with the risk of recurrent events in patients who have already survived a first stroke.[16]

CONCLUSION

Stroke recurrence rates remain high in sub-Saharan Africa, with risk factors such as hypertension, alcohol consumption, diabetes mellitus, female gender, non-adherence to treatment, and cardiac causes being the main risk factors. Antiplatelet therapy is an important treatment for stroke prevention, but its effectiveness varies among different ethnic groups. Triticagrelor may be more effective than aspirin for patients with aortic arch and intracranial atherosclerotic disease, but it is important to consider the patient's bleeding risk before prescribing this medication. DAPT (dual antiplatelet therapy) is effective in preventing stroke in patients with intracranial arterial disease (ICAD), but further research is needed to evaluate its effectiveness. Statin-based therapies have been linked to a 12% lower risk of recurrent stroke and a 17% reduced risk of MACE, but there is a 46% increased risk of hemorrhagic stroke and a higher risk for new-onset diabetes. Vitamin D plays a crucial role in brain development, function, and maintenance, providing a neuroprotective effect against age-related brain degeneration.

REFERENCES

[1] Campbell, B. C. V., & Khatri, P. (2020). Stroke. The Lancet, 396(10244), 129–142. https://doi.org/10.1016/S0140-6736(20)31179-X

[2] 2. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021 Oct;20(10):795-820. doi: 10.1016/S1474-4422(21)00252-0. Epub 2021 Sep 3. PMID: 34487721; PMCID: PMC8443449..

[3] 3. Mbalinda, S., Kaddumukasa, M., Najjuma, J., Kaddumukasa, M., Nakibuuka, J., Burant, C., Moore, S., Blixen, C., Katabira, E., & Sajatovic, M. (2024). Stroke Recurrence Rate and Risk Factors Among Stroke Survivors in Sub-Saharan Africa: A Systematic Review. Neuropsychiatric Disease and Treatment, Volume 20(April), 783–791. https://doi.org/10.2147/ndt.s442507

[4] 4. O'Donnell, M. J., Chin, S. L., Rangarajan, S., Xavier, D., Liu, L., Zhang, H., Rao-Melacini, P., Zhang, X., Pais, P., Agapay, S., Lopez-Jaramillo, P., Damasceno, A., Langhorne, P., McQueen, M. J., Rosengren, A., Dehghan, M., Hankey, G. J., Dans, A. L., Elsayed, A., … Yusuf, S. (2016). Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. The Lancet, 388(10046), 761–775. https://doi.org/10.1016/S0140-6736(16)30506-2

[5] 5. Maredza, M., Bertram, M. Y., Gómez-Olivé, X. F., & Tollman, S. M. (2016). Burden of stroke attributable to selected lifestyle risk factors in rural South Africa Global health. BMC Public Health, 16(1). https://doi.org/10.1186/s12889-016-2805-7

[6] 6. Sandercock PA, Counsell C, Kane EJ. Anticoagulants for acute ischaemic stroke. Cochrane Database Syst Rev. 2015 Mar 12;2015(3):CD000024. doi: 10.1002/14651858.CD000024.pub4. Update in: Cochrane Database Syst Rev. 2021 Oct 22;10:CD000024. PMID: 25764172; PMCID: PMC7065522.

[7] 7. Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Connors, J. J., Culebras, A., Elkind, M. S. V., George, M. G., Hamdan, A. D., Higashida, R. T., Hoh, B. L., Janis, L. S., Kase, C. S., Kleindorfer, D. O., Lee, J. M., Moseley, M. E., Peterson, E. D., Turan, T. N., Valderrama, A. L., & Vinters, H. V. (2013). An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American heart association/American stroke association. Stroke, 44(7), 2064–2089. https://doi.org/10.1161/STR.0b013e318296aeca

[8] 8. Li, G., Li, L., Adachi, J. D., Wang, R., Ye, Z., Liu, X., Thabane, L., & Lip, G. Y. H. (2022). Relationship between Serum 25-Hydroxyvitamin D Level and Risk of Recurrent Stroke. Nutrients, 14(9), 1–10. https://doi.org/10.3390/nu14091908

[9] 9. Flach, C., Muruet, W., Wolfe, C. D. A., Bhalla, A., & Douiri, A. (2020). Risk and Secondary Prevention of Stroke Recurrence: A Population-Base Cohort Study. Stroke, 51(8), 2435–2444. https://doi.org/10.1161/STROKEAHA.120.028992

[10] 10. Feigin, V. L., Forouzanfar, M. H., Krishnamurthi, R., Mensah, G. A., Bennett, D. A., Moran, A. E., Sacco, R. L., Anderson, L., Donnell, M. O., Venketasubramanian, N., Barker-collo, S., Lawes, C. M. M., Wang, W., Shinohara, Y., Witt, E., & Ezzati, M. (2014). from the Global Burden of Disease Study 2010. 383(9913), 245–254.

[11] 11. Adoukonou, T., Kossi, O., Fotso Mefo, P., Agbétou, M., Magne, J., Gbaguidi, G., Houinato, D., Preux, P. M., & Lacroix, P. (2021). Stroke case fatality in sub-Saharan Africa: Systematic review and meta-analysis. International Journal of Stroke, 16(8), 902–916. https://doi.org/10.1177/1747493021990945

[12] 12. Owolabi, M. O., Akarolo-Anthony, S., Akinyemi, R., Arnett, D., Gebregziabher, M., Jenkins, C., Tiwari, H., Arulogun, O., Akpalu, A., Sarfo, F. S., Obiako, R., Owolabi, L., Sagoe, K., Melikam, S., Adeoye, A. M.,

Lackland, D., & Ovbiagele, B. (2015). The burden of stroke in Africa: A glance at the present and a glimpse into the future. Cardiovascular Journal of Africa, 26(2), S27–S38. https://doi.org/10.5830/CVJA-2015-038

[13] 13. Akinyemi, R. O., Owolabi, M. O., Ihara, M., Damasceno, A., Ogunniyi, A., Dotchin, C., Paddick, S. M., Ogeng'o, J., Walker, R., & Kalaria, R. N. (2019). Stroke, cerebrovascular diseases and vascular cognitive impairment in Africa. Brain Research Bulletin, 145, 97–108. https://doi.org/10.1016/j.brainresbull.2018.05.018

[14] 14. Akinyemi, R. O., Ovbiagele, B., Adeniji, O. A., Sarfo, F. S., Abd-Allah, F., Adoukonou, T., Ogah, O. S., Naidoo, P., Damasceno, A., Walker, R. W., Ogunniyi, A., Kalaria, R. N., & Owolabi, M. O. (2021). Stroke in Africa: profile, progress, prospects and priorities. Nature Reviews Neurology, 17(10), 634–656. https://doi.org/10.1038/s41582-021-00542-4

[15] 15. Lin, B., Zhang, Z., Mei, Y., Wang, C., Xu, H., Liu, L., & Wang, W. (2021). Cumulative risk of stroke recurrence over the last 10 years: a systematic review and meta-analysis. Neurological Sciences, 42(1), 61–71. https://doi.org/10.1007/s10072-020-04797-5

[16] 16. Vergatti, A., Abate, V., Zarrella, A. F., Manganelli, F., Tozza, S., Iodice, R., De Filippo, G., D'Elia, L., Strazzullo, P., & Rendina, D. (2023). 25-Hydroxy-Vitamin D and Risk of Recurrent Stroke: A Dose Response Meta-Analysis. Nutrients, 15(3), 1–12. https://doi.org/10.3390/nu15030512

[17] 17. Kolmos, M., Christoffersen, L., & Kruuse, C. (2021). Recurrent Ischemic Stroke – A Systematic Review and Meta-Analysis. Journal of Stroke and Cerebrovascular Diseases, 30(8). https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105935

[18] 18. Shah, J., Liu, S., & Yu, W. (2022). Contemporary antiplatelet therapy for secondary stroke prevention: a narrative review of current literature and guidelines. Stroke and Vascular Neurology, 7(5), 406–414. https://doi.org/10.1136/svn-2021-001166

[19] 19. Grory, B. Mac, Yaghi, S., Cordonnier, C., Sposato, L. A., Romano, J. G., & Chaturvedi, S. (2022). Advances in recurrent stroke prevention: Focus on antithrombotic therapies. Circulation Research, 130(8), 1075–1094. https://doi.org/10.1161/CIRCRESAHA.121.319947

[20] 20. Lee, M., Cheng, C. Y., Wu, Y. L., Lee, J. Der, Hsu, C. Y., & Ovbiagele, B. (2022). Association Between Intensity of Low-Density Lipoprotein Cholesterol Reduction With Statin-Based Therapies and Secondary Stroke Prevention A Meta-analysis of Randomized Clinical Trials. JAMA Neurology, 79(4), 349–358. https://doi.org/10.1001/jamaneurol.2021.5578

[21] 21. Bangad, A., Abbasi, M., & de Havenon, A. (2023). Secondary Ischemic Stroke Prevention. Neurotherapeutics, 20(3), 721–731. https://doi.org/10.1007/s13311-023-01352-w

[22] 22. Mbonda, P.-C., Mafo, D., Doumbe, J., & Kuate, C. (2021). Recurrence of Strokes and Associated Factors at Laquintinie Hospital in Douala. Clinical Neurology and Neuroscience, 5(3), 46. https://doi.org/10.11648/j.cnn.20210503.12

[23] 23. Han, J., Mao, W., Ni, J., Wu, Y., Liu, J., Bai, L., Shi, M., Tu, J., Ning, X., & Wang, J. (2020). Rate and Determinants of Recurrence at 1 Year and 5 Years After Stroke in a Low-Income Population in Rural China. Frontiers in Neurology, 11(January), 1–9. https://doi.org/10.3389/fneur.2020.00002

[24] 24. Prabhakaran, S., Liebeskind, D. S., Cotsonis, G., Nizam, A., Feldmann, E., Sangha, R. S., Campo-Bustillo, I., & Romano, J. G. (2021). Predictors of Early Infarct Recurrence in Patients with Symptomatic Intracranial Atherosclerotic Disease. Stroke, 52(6), 1961–1966. https://doi.org/10.1161/STROKEAHA.120.032676

[25] 25. Wang, Y., Meng, X., Wang, A., Xie, X., Pan, Y., Johnston, S. C., Li, H., Bath, P. M., Dong, Q., Xu, A., Jing, J., Lin, J., Niu, S., Wang, Y., Zhao, X., Li, Z., Jiang, Y., Li, W., Liu, L., … Wang, B. (2021). Ticagrelor versus Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA . New England Journal of Medicine, 385(27), 2520–2530. https://doi.org/10.1056/nejmoa2111749

[26] 26. Amarenco, P., Denison, H., Evans, S. R., Himmelmann, A., James, S., Knutsson, M., Ladenvall, P., Molina, C. A., Wang, Y., & Claiborne Johnston, S. (2020). Ticagrelor Added to Aspirin in Acute Nonsevere Ischemic Stroke or Transient Ischemic Attack of Atherosclerotic Origin. Stroke, 51(12), 3504–3513. https://doi.org/10.1161/STROKEAHA.120.032239

[27] 27. Liu, L., Wong, K. S. L., Leng, X., Pu, Y., Wang, Y., Jing, J., Zou, X., Pan, Y., Wang, A., Meng, X., Wang, C., Zhao, X., Soo, Y., Claiborne Johnston, S., & Wang, Y. (2015). Dual antiplatelet therapy in stroke and ICAS. Neurology, 85(13), 1154–1162. https://doi.org/10.1212/WNL.0000000000001972

[28] 28. Tan, C. H., Wu, A. G. R., Sia, C. H., Leow, A. S. T., Chan, B. P. L., Sharma, V. K., Yeo, L. L. L., & Tan, B. Y. Q. (2021). Cilostazol for secondary stroke prevention: Systematic review and meta-analysis. Stroke and Vascular Neurology, 6(3), 410–423. https://doi.org/10.1136/svn-2020-000737

[29] 29. Violi, F., Calvieri, C., Ferro, D., & Pignatelli, P. (2013). Statins as antithrombotic drugs. Circulation, 127(2), 251–257. https://doi.org/10.1161/CIRCULATIONAHA.112.145334

[30] 30. Kleindorfer, D. O., Towfighi, A., Chaturvedi, S., Cockroft, K. M., Gutierrez, J., Lombardi-Hill, D., Kamel, H., Kernan, W. N., Kittner, S. J., Leira, E. C., Lennon, O., Meschia, J. F., Nguyen, T. N., Pollak, P. M., Santangeli, P., Sharrief, A. Z., Smith, S. C., Turan, T. N., & Williams, L. S. (2021). 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. In Stroke (Vol. 52, Issue 7). https://doi.org/10.1161/STR.0000000000000375

[31] 31. Muscogiuri, G., Annweiler, C., Duval, G., Karras, S., Tirabassi, G., Salvio, G., Balercia, G., Kimball, S., Kotsa, K., Mascitelli, L., Bhattoa, H. P., & Colao, A. (2017). Vitamin D and cardiovascular disease: From atherosclerosis to myocardial infarction and stroke. International Journal of Cardiology, 230, 577–584. https://doi.org/10.1016/j.ijcard.2016.12.053