Original Article

Does Statin Increase the Risk of Intracerebral Hemorrhage?

Ahmed Elsayed Ahmed[1], Khalid Ahmed Albedaiwi[2*], Basil Ahmed B Albarrak[2], Abdullah Kareem S Alkhabur[2], Sultan Naif Alhudaib[2], Abdulkareem Ali M Alyousef[2], Abdulelah Sultan I Alenad[2], Abdulaziz Saad Aljurayyad[3], Bader Hammad Alharbi[3], Abdullah Zuhair ALsheri[4], Alanoud Dera Alqahtani[5]

[1]Faculty of Medicine, Al Mouwasat Hospital, Al Khobar, Saudi Arabia. [2]Faculty of Medicine, Women's Maternity & Children Hospital, Sakaka, Saudi Arabia. [3]Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia. [4]Faculty of Pharmacy, Maternity and Children Hospital, Tabuck, Saudi Arabia. [5]Faculty of Medicine, Najran University, Najran, Saudi Arabia.

Abstract

Intracerebral hemorrhage (ICH) is a neurological condition associated with substantial health challenges and a high rate of morbidity and mortality. Statins have a crucial role in preventing both initial and recurrent cardiovascular and cerebrovascular ischemic events. While the benefits of statins in reducing the risk of ischemic stroke are well-established, some post hoc analyses of studies have raised questions about a potential connection between statin therapy and the development of ICH. This possible increase in the risk of ICH is believed to be related to the direct pharmacological impact of lowering total cholesterol and low-density lipoprotein levels in the bloodstream, along with the additional pleiotropic effects of statins. The Medline, Pubmed, Embase, NCBI, and Cochrane databases were searched for studies of patients with non-alcoholic fatty liver disease. Incidence, etiology, and management options were analyzed. The use of statin therapy in individuals who have experienced a stroke was found to elevate the risk of hemorrhagic stroke, yet it effectively lowered the risk of ischemic strokes. When considering both the advantages and possible drawbacks, statin therapy has an overall positive impact on individuals with a history of stroke or transient ischemic attack (TIA). Nevertheless, further research is necessary to establish the definitive implications of the heightened risk of hemorrhagic stroke that our study has uncovered.

Keywords: High-dose statin hyperlipidemia, Intracerebral hemorrhage, Ischemic stroke, Statin

Introduction

Statin therapy has been a standard approach for reducing cholesterol production and preventing cardiovascular issues for the past 30 years [1]. Most world guidelines recommend their use to reduce the possibility of cardiovascular events and stroke in individuals affected with cerebrovascular disease [2]. Despite the proven benefits of statins in initial stroke prevention, their prescription rates are suboptimal, varying with age, gender, race, and location. Some of this hesitancy is due to concerns for patients with a history of intracerebral hemorrhage (ICH), as these patients would be put at greater risk of the same [3]. Two important clinical trials—the Heart Protection Study (HPS) and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)—have found that the potential benefits of lowering recurrent ischemic stroke are outweighed by the increased risk of hemorrhagic stroke associated with statins. It may be better to avoid statins in cases of lobar ICH, according to a risk study of statin medication in patients with a prior ICH. However, there was no discernible association between statins and ICH in trials with people who had never had a stroke. Early neurological improvement at the 6-month point has been linked to statin medication following an ICH [4]. Therefore, statins may be beneficial for those who have had a stroke, and more research is required to clear up any doubts about potential negative effects [5].

Risk Factors and Epidemiology

Intracerebral hemorrhage (ICH), which accounts for ten to twenty percent of all strokes worldwide, is a serious medical concern. Indeed, ICH is estimated at 24.6 cases per 100,000 individual-years [6]. Key risk factors for this event are advancing age, amyloid angiopathy, and hypertension, while other contributing factors are male gender, diabetes, cocaine use, the use of drugs that affect blood clotting, smoking, and

Address for correspondence: Khalid Ahmed Albedaiwi, Faculty of Medicine, Women's Maternity & Children Hospital, Sakaka, Saudi Arabia.
Khaled2797@yahoo.com

How to cite this article: Ahmed AE, Albedaiwi KhA, Albarrak BAB, Alkhabur AKS, Alhudaib SN, Alyousef AAM, et al. Does Statin Increase the Risk of Intracerebral Hemorrhage?. Arch Pharm Pract. 2023;14(S):A06231533.

alcohol consumption [7]. Multiple risk factors can combine, elevating an individual's likelihood of experiencing ICH. ICH typically occurs in many brain areas, involving the cerebellum, thalamus, brain stem, basal ganglia, and cerebral lobes [8]. It arises when small arteries branching off the basilar and cerebral arteries rupture and is associated with a significant mortality risk: the survival rate for 1 year is approximately 46%, and for 5 years it drops to 29%. Thus, there is a growing interest among clinicians in exploring potential therapies that could protect the brain because of the high morbidity and mortality rate associated with this event [9].

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, more often regarded as statins, are medications that primarily lower cholesterol levels by competitively and reversibly inhibiting HMG-CoA reductase, a critical enzyme in cholesterol production [10]. This cholesterol-lowering mechanism has been shown to reduce cardiovascular events and ischemic strokes in patients with coronary artery disease. Beyond their cholesterol-lowering properties, statins also exhibit various other beneficial effects, including antithrombotic, antioxidative, neuroprotective, and anti-inflammatory actions, as demonstrated both in animal and patient population studies [11].

Treatment

Although all statins work by competitively and reversibly inhibiting HMG-CoA reductase, there are notable distinctions among these drugs within the statin class. In the United States, there are seven available statins: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin [12]. These variations in drug properties can influence the potential benefits and risks of statin therapy in cases of intracerebral hemorrhage (ICH).

The ability of statins to cross the blood-brain barrier and enter the cerebral cortex is directly linked to their lipophilic characteristics. Studies in mice assessed the concentrations of simvastatin, lovastatin, and pravastatin within the cerebral cortex, revealing that simvastatin had the highest concentration, followed by lovastatin and pravastatin. This aligns with their partition coefficient (logD), with lovastatin and simvastatin being the most lipophilic. Besides pharmacokinetic properties, it is important to consider the relative potency of low-density lipoprotein (LDL) reduction among statins. Two pivotal trials evaluated the relative potency based on the change in percentage of LDL from baseline: rosuvastatin is the most potent, followed by atorvastatin, pitavastatin, simvastatin, lovastatin, pravastatin, and Fluvastatin [13]. While discontinuation rates of statins due to side effects observed in clinical trials have been similar to those for placebos, it is crucial to be aware of potential clinical risks before initiating statin therapy. In the general population, 1% of patients on statins have presented asymptomatic elevations in liver enzymes, and this is dose-dependent [13]. Myopathy, a rare side effect with an incidence rate below 0.1%, can progress to a severe condition called rhabdomyolysis if left untreated. Even though potential risks of statin therapy can be inferred from critically ill patients, there is nonetheless limited data on the safety profile of statin therapy in ICH patients. Additionally, drug interactions also need consideration for individuals on statin therapy. Most statins are metabolized through cytochrome P450 enzymes, making it essential to account for interactions, as some medications can reduce statin effectiveness, while others may increase the risk of adverse effects. If discontinuing the interacting medication is not an option, it is advisable to opt for a statin that has less risk of interacting [14].

Results and Discussion

Epidemiological studies have suggested a higher occurrence of hemorrhagic stroke and increased mortality from intracerebral hemorrhage (ICH) in populations with low cholesterol levels [15]. This has raised the hypothesis that cholesterol might play a role in maintaining the integrity of cerebrovascular walls, and low levels could potentially increase the chances of ICH and vessels rupturing. Additionally, some research has linked hemorrhagic stroke with the use of statins. For example, the SPARCL trial, which employed high-dose atorvastatin for secondary stroke prevention, noted a greater incidence of ICH compared to a placebo.

strokes had their risk of hemorrhagic stroke increase two-fold [16]. However, previous meta-analyses of statin therapy didn't find a heightened risk of hemorrhagic stroke. To shed light on this, a comprehensive meta-analysis was conducted, involving 31 randomized clinical trials. The analysis revealed that active statin therapy was responsible for a minor, statistically insignificant increase in risk of ICH. Interestingly, this slight increase in ICH risk was not linked to the effects of statin therapy on LDL cholesterol levels. Instead, it suggests that any potential risk of ICH might be due to other effects of statin therapy, unrelated to LDL [17]. When the analysis was divided based on the type of prevention (secondary vs. primary), secondary prevention studies displayed a trend towards higher chances of ICH compared to primary prevention studies. This indicates that patients with previous strokes might be at a somewhat increased risk of hemorrhagic stroke [18].

Clinicians should exercise caution in their treatment of such patients with statins, especially those with a history of lobar hemorrhage, as further research is needed. The study acknowledged some limitations, such as the absence of patient-level data and the possibility that prior trials reporting hemorrhagic stroke rates might have included other types of intracranial bleeding, apart from ICH. Nevertheless, statin therapy is not significantly associated with an increased risk of ICH, and the benefits of statins in reducing overall stroke and mortality outweigh any minimal increase in the increased potential for ICH. Consequently, the current

recommendations to prescribe statins to the right patients remain supported [19].

Conclusion

Statin therapy is widely utilized and endorsed by guidelines in multiple disciplines for preventing arteriosclerotic cardiovascular disease and reducing the risk of ischemic strokes, both in primary and secondary prevention. Despite concerns about potential mechanisms that could raise the risk of intracerebral hemorrhage (ICH), as well as findings from the SPARCL trial's post hoc analysis, the growing body of evidence contradicts the notion that statins increase ICH rates in any significant manner. While there is mixed data regarding the relationship between decreased total cholesterol and LDL levels and a heightened risk of ICH, this risk is not consistently linked to statin usage. To clarify which patients with ICH would benefit from statin therapy, further research is necessary. As a result, the decision to implement statin therapy in patients with a history of ICH or those at risk should be made on a case-by-case basis. Statin therapy should be advised in cases where the potential benefits are likely to outweigh the risks.

ACKNOWLEDGMENTS: None
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: None
ETHICS STATEMENT: None

References

1. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke. 2014;9(7):840-55.
2. Cordenier A, De Smedt A, Brouns R, Uyttenboogaart M, De Raedt S, Luijckx GJ, et al. Pre-stroke use of statins on stroke outcome: a meta-analysis of observational studies. Acta Neurol Belg. 2011;111(4):261-7.
3. Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Statin use following intracerebral hemorrhage: a decision analysis. Arch Neurol. 2011;68(5):573-9.
4. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.
5. Tapia-Pérez JH, Rupa R, Zilke R, Gehring S, Voellger B, Schneider T. Continued statin therapy could improve the outcome after spontaneous intracerebral hemorrhage. Neurosurg Rev. 2013;36(2):279-87.
6. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;2013(1):CD004816.
7. Siniscalchi A, Bonci A, Mercuri NB, De Siena A, De Sarro G, Malferrari G, et al. Cocaine dependence and stroke: pathogenesis and management. Curr Neurovasc Res. 2015;12(2):163-72.
8. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med. 2001;344(19):1450-60.
9. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005;19(1):117-25.
10. Willey JZ, Elkind MS. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the treatment of central nervous system diseases. Arch Neurol. 2010;67(9):1062-7.
11. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2014;85(6):660-7.
12. Thelen KM, Rentsch KM, Gutteck U, Heverin M, Olin M, Andersson U, et al. Brain cholesterol synthesis in mice is affected by high dose of simvastatin but not of pravastatin. J Pharmacol Exp Ther. 2006;316(3):1146-52.
13. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol. 2003;92(2):152-60.
14. Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD; STASH Collaborators. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol. 2014;13(7):666-75.
15. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N Engl J Med. 1989;320(14):904-10.
16. Björkhem I, Meaney S. Brain cholesterol: long secret life behind a barrier. Arterioscler Thromb Vasc Biol. 2004;24(5):806-15.
17. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol. 2009;8(5):453-63.
18. Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Statin use following intracerebral hemorrhage: a decision analysis. Arch Neurol. 2011;68(5):573-9.
19. Goldstein MR, Mascitelli L, Pezzetta F. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology. 2009;72(16):1448; author reply 1448-9.