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The Role of Statins in Stroke Management

Research Article

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Abstract

Stroke is the second leading cause of death globally. Statins are the preferred drugs for management of dyslipidemia, a major risk factor for atherosclerosis. In addition to their cholesterol-lowering effects, statins have been shown to have pleiotropic effect of being antithrombotic, anti-inflammatory, and providing endothelial protection. The present review was performed to assess the role of statins in the prevention and management of stroke.

A PubMed search was conducted with the search terms 'statins' and 'stroke' for randomized controlled trials published between 2010 and 2020. Abstracts were screened and relevant articles were selected. A search was then conducted on PubMed and Google Scholar with the search terms 'statins', 'stroke', 'primary prevention', 'secondary prevention', between 2010 and 2020 and relevant articles were selected. In a backward chronological search, the reference lists of all the selected articles were checked and other relevant articles were selected. The selected papers were used to evaluate the role of statins in the prevention and management of stroke.

The narrative review discusses the role of statins in primary and secondary prevention of stroke, role of intensive statin therapy and the economic implications of statins for the prevention of stroke.

It was concluded that statins have known role in reducing the cholesterol levels, and primary and secondary prevention trials have time and again shown the beneficial effects of statins in the prevention and management of stroke. Treatment with statins could be more cost-effective if low-risk patients are aggressively treated, and guidelines consider the therapy for a broader patient population.

Keywords: Stroke; Statins; Ischemic stroke, Cardiometabolic stroke, Primary prevention, Secondary prevention

Introduction

A cerebrovascular accident (CVA), or an acute stroke, is also termed a 'brain attack' [1]. The aging population and the accruing risk factors on a global level, are contributing to an increasing risk of stroke. The Global Burden of Disease 2016 Lifetime Risk of Stroke Collaborators stated that there has been a relative increase of 8.9% in the lifetime risk of stroke from 1990 to 2016 [2]. Additionally, stroke is the second leading cause of death globally, after ischemic heart disease [3].

It is estimated that close to 17 million people succumb to cardiovascular diseases (CVDs), especially heart attacks and strokes, each year. A vast majority of these deaths can be attributed to tobacco smoking, which tends to heighten the risk of death from coronary heart disease and cerebrovascular disease by about 2-3 times [4].

Additionally, there is a close link between cardiovascular diseases and cerebral perfusion. Any cardiac pathology can play a role in raising the risk of stroke. A stroke may often be the first presentation of an unidentified cardiac disorder [5]. While heart diseases can increase the risk of stroke, acute stroke may also lead to cardiac injury. Around 85% of all cases of stroke are ischemic while 15% are hemorrhagic strokes [5].

Coronary artery disease and stroke are known to share common risk factors. Hypertension is the most significant risk factor for both ischemic and hemorrhagic stroke. Other common risk factors for stroke include cardiac disease, particularly atrial fibrillation; diabetes; smoking; abdominal obesity; diet; physical inactivity; alcohol; raised apolipoprotein ApoB/ApoA1 ratio; and psychosocial factors [5].

Considering the enormous burden that the incidence of stroke poses on individuals and healthcare systems, it is important to consider stroke prevention and management early. Stroke prevention is aimed at reducing stroke incidence by modification of risk factors. Prevention can be categorized into primordial prevention, primary prevention and secondary prevention. Primordial prevention deals with lifestyle modification and includes efforts encouraging smoking cessation, healthy diet, increased physical activity, and weight control. Primary and secondary stroke prevention deal with an individual's specific lifestyle-related and medical risk factors, such as hypertension and diabetes [6].

Statins are the preferred drugs for management of dyslipidemia, a major risk factor for atherosclerosis. Besides their cholesterol-lowering effects, statins have been shown to have pleiotropic effects of being antithrombotic, anti-inflammatory, and providing endothelial protection [7].

This narrative review aims to discuss the role of statins in the prevention and management of stroke and the economic implications of statins for the prevention of stroke.

Methodology

A review of published literature was conducted to determine the role of statins in the prevention and management of stroke. A PubMed search was conducted with the search terms 'statins' and 'stroke' for articles published between 2010 and 2020 and the search returned 370 results (all randomized controlled trials). Abstracts of these articles were checked and 9 of these were selected. A search was then conducted on PubMed and Google Scholar with the search terms 'statins', 'stroke','primary prevention', 'secondary prevention',and the search duration was 2010 to 2020. The abstracts of the searched articles were scanned and final articles were then identified and selected. In a backward chronological search, the reference lists of all selected articles were checked for citations that could not be detected in the primary search and relevant articles were selected (Figure 1).

Information from the selected articles was extracted and an analysis of the selected articles was then conducted by the investigators. Data were extracted after reading the article. Both primary literature and gray literature were screened and selected for the purpose of the review article.

A narrative review was developed based on themes identified on the analysis of the selected articles.

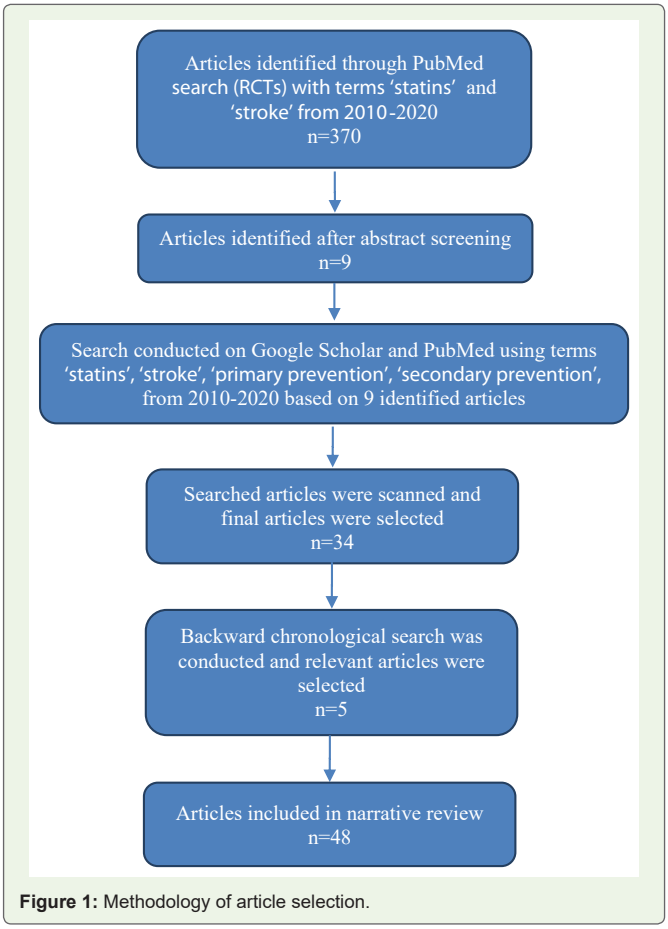

Figure 1: Methodology of article selection.

Results and Discussion

A total of 48 articles were selected. The themes that surfaced after the analysis of selected literature included role of statins in primary and secondary prevention of stroke, role of intensive statin therapy and the economic implications of statins for the prevention of stroke.

Statins in primary prevention of cerebrovascular accident

Raised cholesterol levels are known to heighten the risk for cardiovascular disease, including stroke. Atherosclerosis is a chronic inflammatory disease, with hypertension, raised lipid levels, diabetes, and smoking being the main risk factors [8]. A plaque builds up in the walls of the arteries, causing their narrowing and making it harder for blood to flow. If a blood clot is formed, it stops the blood flow, causing a heart attack or stroke [8].

Therefore, interventions to decrease the cholesterol levels are often resorted to in order to reduce the risk. Statins have proven effect in cholesterol lowering and hence, are often used to prevent cardiovascular events in patients at high risk [9].

While low-density lipoprotein cholesterol (LDL-C) lowering appears to be the leading mechanism by which statins reduce stroke events, additional factors also play a role in stroke reduction. These cholesterol-independent actions have additional cardiovascular benefits [10].

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Statins decrease serum cholesterol level as they inhibit hydroxymethylglutaryl-coenzymeA (HMG-CoA) reductase [11]. Statins are also known to have pleiotropic effects that tend to mediate their beneficial effects. Statins have been reported to have a neuroprotective effect and also improve recovery after stroke [9]. Besides reducing LDL-C levels, statins have the properties of plaque stabilization and endothelial homeostasis; have anti-inflammatory, antioxidant, anti-proliferative and immunomodulatory effects; and prevent platelet aggregation [12].

Therefore, in addition to their cholesterol-lowering effects, the beneficial effects of statins on stroke reduction could be attributed to their pleiotropic benefits.

Treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, i.e., statins, has been shown to reduce the risk of stroke in patients at high risk for atherosclerosis. Leading guidelines recommend the use of statins, besides lifestyle modification, for the primary prevention of stroke, particularly ischemic stroke, in patients with a high 10-year risk for cardiovascular events [13]. Although they were primarily employed to improve cardiovascular outcomes in patients with known coronary artery disease, the use of statins has now become increasingly common in people at low cardiovascular risk. Tonelli and colleagues conducted a comprehensive systematic review of the implications of statin use among low cardiovascular risk individuals, including indirect comparisons of high-potency and low-potency statins [14]. They evaluated the effects of statins for primary prevention in people at low cardiovascular risk. With 29 trials including 80,711 participants in the analysis, patients treated with statins had a significantly lesser likelihood than controls of having nonfatal stroke (relative risk [RR] 0.81, 95% confidence interval [CI] 0.68-0.96), as well as myocardial infarction (RR 0.64, 95% CI 0.49–0.84). All-cause mortality was found to be significantly lower among those who received a statin compared to controls. Low- as well as high-potency statins could prevent death and cardiovascular-related morbidity in individuals at low risk of cardiovascular event [14].

On similar lines, the Cholesterol Treatment Trialists' (CTT) Collaborators had conducted a meta-analysis with 27 randomized trials to assess the impact of lowering LDL-C with statins in people at low risk of vascular disease. They noted that in participants with 5-year risk of major vascular events <10% (RR per 1.0 mmol/L LDL-C reduction 0.76, 99% CI 0.61-0.95, p=0.0012), the reduction in risk for stroke was similar to that observed in higher risk categories (trend p=0.3). The meta-analysis suggested that lowering LDL-C with standard statin therapy led to a reduction in the 5-year incidence of major coronary events, coronary revascularizations, as well as ischemic strokes by about one-fifth for every 1.0 mmol/L reduction in LDL-C [15].

Investigators for the landmark trial - Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) - noted that the previous primary prevention trials of statin therapy using the cholesterol criteria for enrolling patients did not report significant reductions in stroke risk. The investigators thus assessed if statin therapy could reduce stroke rates among individuals with low cholesterol but raised high-sensitivity C-reactive protein (hs-CRP). They evaluated 17,802 apparently healthy individuals with LDL-C levels <130 mg/dL and hs-CRP levels >2.0 mg/L. Participants were randomized to receive rosuvastatin 20 mg daily or placebo and followed-up for the occurrence of a first stroke. Statin therapy led to a 48% reduction in the hazard of fatal and nonfatal stroke, following a median follow-up of 1.9 years (maximum, 5.0 years), in comparison with placebo, for an incidence rate of 0.18 and 0.34 per 100 person-years of observation, respectively (hazard ratio 0.52; 95% confidence interval, 0.34 to 0.79; P=0.002). This was attributed to a 51% decline in the rate of ischemic stroke (hazard ratio, 0.49; 95% confidence interval, 0.30 to 0.81; P=0.004). There was no difference in the rates of hemorrhagic stroke between the active and placebo groups (hazard ratio, 0.67; 95% confidence interval, 0.24 to 1.88; P=0.44). Statin therapy, therefore, reduced the incidence of ischemic stroke by over 50% among individuals with low levels of LDL-C who were at risk on account of elevated levels of hs-CRP [16].

Considering the limitations of several trials for not being able to determine the difference in individual endpoints, ameta-analysis was designed by Chan et al with the aim to have the required power to identify a difference for individual endpoints, including stroke events, major coronary events, and deaths related to CVD or coronary heart disease (CHD), and evaluate drug-related adverse events in studies looking into the results of intensive lipid lowering by statins. The findings revealed that among individuals at high risk of cardiovascular events, intensive lipid lowering with statins to LDL-C level <2.1 mmol/l led to a significant reduction in risk of stroke, major coronary events and CVD or CHD deaths compared to LDL-C level ≥ 2.1 mmol/l. In the intensive treatment arm, the odds ratio (OR) for stroke was 0.80 (95% CI 0.71-0.89), for major coronary events was 0.74 (95% CI 0.65-0.83), and for CVD or CHD deaths was 0.84 (95% CI 0.74-0.95). The results of this meta-analysis took the evidence further by showing that individual endpoints are reduced by using high-dose statins to decrease LDL-C to <2.1 mmol/l.17

Rheumatoid arthritis (RA) is a condition that is known to be associated with increased risk of a cardiovascular event (CVE). The role of statins in this patient population is not well understood. Therefore, a recent randomized placebo-controlled trial assessed if statin therapy is better than placebo for the primary prevention of CVEs in RA patients. Investigators followed 3,002 patients (mean age 61 years; 74% female) for a median of 2.51 years. The primary end point comprised of a composite of cardiovascular death, myocardial infarction, stroke, transient ischemic attack (TIA), or arterial revascularization. Around 1.6% of the patients receiving statin experienced a primary end point, compared to 2.4% of those receiving placebo. Presumed ischemic stroke or TIA was noted in 0.4% of the patients receiving statin compared to 0.8% of the patients in the placebo group. The trial suggested that statin therapy is safe for primary prevention of CVEs in patients with RA and may confer similar risk reduction in this population as in other populations [18].

Of note, there is a possibility that statin therapy might increase the risk of hemorrhagic stroke. However, it has been noted that the annual excess risk of hemorrhagic strokes per 1.0 mmol/L decrease in LDL-C might be around 0.5 per 1000 people treated over a period of 5 years and it is noteworthy that statin therapy leads to a reduction in overall stroke independent of the predicted risk. Therefore, an

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increase in hemorrhagic stroke risk is outweighed by the reduced risk of ischemic stroke, besides reduction in other occlusive vascular events and deaths, even in those with 5-year risk of major vascular events < 5%.15

Additionally, in the JUPITER primary prevention trial, the cardiovascular and mortality benefits of statin therapy outpaced the diabetes hazard, including in subjects at high risk of developing diabetes [19].

All the evidence that has been cited above thus seems to suggest that statin therapy is an effective and safe treatment option for primary prevention of stroke in different patient populations, and in low-risk patients as well. Table 1 summarizes the findings from the articles included in the review in terms of primary prevention of stroke.

Statins in secondary prevention of stroke

Role of statins in ischemic stroke

Statins are the recommended treatment option for primary and secondary stroke prevention. Several large randomized, double-blind trials have demonstrated that the use of statins in ischemic stroke reduces the risk of incident and recurrent stroke [11].

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline also recommends the use of statins for decreasing the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA that appear to have atherosclerotic origin [20]. Statins have been shown to diminish the incidence of ischemic stroke time and again. This finding emphasizes on their non-cholesterol lowering effects as serum cholesterol is poorly correlated with the risk for ischemic stroke [21].

The pleiotropic effects of statins on recurrent stroke are still not clearly understood. Therefore, Kitagawa and colleagues assessedhs-CRP levels during follow-ups with regard to stroke recurrence and incident vascular events [22]. They studied the effects of statin therapy on hs-CRP in ischemic stroke, and also looked into the impact of hs-CRP on recurrent stroke and vascular events. In the statin group, hs-CRP levels exhibited a significant reduction after 2 months (median 592 μg/L), and continued to be significantly lower till study end. In the control group, baseline hs-CRP was similar to the value after 2 months. Thus, in non-cardiogenic ischemic stroke, treatment with statins may reduce vascular inflammation as evidenced by hs-CRP.22 of note, hs-CRP, a non-specific marker of inflammatory diseases, is an independent risk predictor of cardiovascular diseases [12]. The study by Kitagawa et al is the first to demonstrate the anti-inflammatory effects of statins in a randomized larger-scale set up among patients with chronic ischemic stroke. The data from this study support guideline recommendations of statin treatments for prevention of stroke recurrence [22].

Additional evidence of the benefit of statins in reducing the risk of ischemic stroke comes from a recent systematic review and network meta-analysis including 9 trials which looked at randomized controlled trials (RCTs) that evaluated statins in patients with ischemic stroke or TIA up to July 2017. Statin therapy was tied to a reduced risk of ischemic stroke, ischemic stroke or TIA, as well as a cardiovascular event. The meta-analysis suggested that the use of statins is safe [20].

A prospective cohort study included consecutive patients diagnosed with an ischemic stroke and aimed to provide real-world data for the associations between secondary prevention of stroke and statin use. Patients without statin use had a greater risk of stroke recurrence as well as worse functional outcomes. Those with poor adherence to statins or discontinuation of the treatment had worse prognosis after stroke while early onset of statin use was associated with better outcomes. The study concluded that statins have a vital role in treating ischemic stroke, preventing stroke recurrence and cardiovascular events, and can also enhance functional performance [23].

Accumulating evidence from trials like Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) and Treat Stroke to Target (TST) also support the role of lipid management with statins in ameliorating ischemic stroke recurrence among patients with a history of ischemic stroke or TIA [24].

Statins are known to improve outcomes after stroke. These agents have been shown to improve infarct volume and neurological outcome in animal models, though data from clinical studies have been

Table 1: Statins for primary prevention of stroke.

Tonelli et al, 2011 Meta-analysis [14]	People at low cardiovascular risk	Statins significantly reduced the likelihood of having nonfatal stroke (RR 0.81, 95% CI 0.68-0.96), myocardial infarction (RR 0.64, 95% CI 0.49-0.84), and all-cause mortality (RR 0.90, 95% CI 0.84-0.97) for trials with a 10-year risk of cardiovascular disease < 20% and 0.83, 95% CI 0.73-0.94, for trials with 10-year risk < 10%, compared to controls
Cholesterol Treatment Trialists (CTT) Collaborators, 2012 Meta-analysis [15]	People at low risk of vascular disease	In subjects with 5-year risk of major vascular events <10% (RR per 1.0 mmol/L LDL cholesterol reduction 0.76, 99% CI 0.61-0.95, p=0.0012), stroke risk reduction was similar to that observed in higher risk categories
Everett et al, 2010 Randomized, double-blind, placebo-controlled multicenter trial [16]	Apparently healthy individuals with low levels of cholesterol but raised high-sensitivity C-reactive protein	48% reduction in the hazard of fatal and nonfatal stroke with statin therapy, compared with placebo (incidence rate, 0.18 and 0.34 per 100 person-years of observation, respectively; hazard ratio 0.52; 95% confidence interval, 0.34 to 0.79; P=0.002); 51% decline in the rate of ischemic stroke (hazard ratio, 0.49; 95% confidence interval, 0.30 to 0.81; P=0.004)
Chan et al, 2011 [17] Meta-analysis	People at high risk of vascular events	Intensive lipid lowering with statins to LDL-C level <2.1 mmol/l led to a significant reduction in risk of stroke, major coronary events and CVD or CHD deaths compared to LDL-C level ≥ 2.1 mmol/l; OR for stroke was 0.80 (95% CI 0.71-0.89), for major coronary events was 0.74 (95% CI 0.65-0.83), for CVD or CHD deaths was 0.84 (95% CI 0.74-0.95)
Kitas et al, 2019 Randomized, double-blind, placebo-controlled trial [18]	Patients with RA	Presumed ischemic stroke/TIA was noted in 0.4% of the patients receiving statin therapy compared to 0.8% of the patients in the placebo group

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inconclusive. The North Dublin Population Stroke Study, therefore, explored the relationship between statin therapy and ischemic stroke outcome. Investigators hypothesized that statin treatment initiated prior to stroke onset and started acutely after ischemic stroke, would lead to greater survival and improved functional outcome, and as hypothesized, statin therapy at stroke onset and newly initiated statin therapy were associated with improved early and late outcomes. Logistic regression analysis, after adjustment for age, prestroke disability (modified Rankin scale), National Institutes of Health Stroke Scale (NIHSS) score, hypertension, and aspirin use, revealed that new post-stroke statin treatment had an independent association with improvement in early and late survival, in comparison with patients not treated with statins. Similar findings could be seen for statin therapy prior to stroke onset [25].

Flint and colleagues also assessed if statin use is tied to improved discharge disposition after ischemic stroke. It was noted that statin users, before and during stroke hospitalization, had higher odds of having a good discharge outcome (OR for discharge to home = 1.38, 95% CI 1.25–1.52, $p < 0.001$; OR for discharge to home or institution = 2.08, 95% CI 1.72–2.51, $p < 0.001$).26A systematic review and meta-analysis looking into the relationship between statin therapy and outcome after ischemic stroke also revealed that statin therapy at stroke onset was associated with improved outcome [27].

Besides being effective in secondary prevention of ischemic stroke, statins are also a safe class of drugs. The most conservative analysis has revealed that statins might have a link with an increased relative risk of hemorrhagic stroke of about 50%. However, only a minority of patients, i.e., <2%, would be exposed to the increased risk, which would correspond to an absolute risk increase of only 0.6%. Interestingly, the raised risk of hemorrhagic stroke is primarily attributed to data obtained from the SPARCL trial wherein there seems to be a failure to maintain the integrity of the treatment intervention over time. Therefore, the observation could possibly be an artifact [20]. Additionally, Heo and colleagues assessed the effect and safety of statin therapy in patients with acute stroke and noted that hemorrhagic infarction or parenchymal/subarachnoid hemorrhage occurred less often in the statin group compared to the placebo group. Statin use was thus found to be safe and decreased hemorrhagic transformation [28].

Available evidence therefore clearly points to the beneficial effects of post-stroke statin therapy in ischemic stroke and suggest that they are safe. Table 2 summarizes the findings from the articles included in the review for secondary prevention of ischemic stroke.

Preventive and therapeutic role of statins in cardioembolic stroke

Evidence is scarce on the administration of statins in patients with cardioembolic stroke.Cardioembolic stroke appears to be associated with atherosclerotic disease, either directly, such as in myocardial infarction, or indirectly, such as in cases of atrial fibrillation (AF), cardiomyopathy, and left ventricular wall thrombus. Statins appear to have an impact on the outcomes of cardioembolic stroke [29].

Atrial fibrillation is a risk factor for cardioembolic stroke. Statins prevent AF, possibly by a reduction in inflammation, as markers such as C-reactive protein are elevated in AF and are reduced by statins [30].

Statins have pleiotropic effects on atherosclerotic plaque stabilization. Collateral status in patients with AF-related stroke is poor as emboli tend to block a large proximal artery. Use of statins in AF patients has been shown to be linked with excellent collateral flow [31]. However, there have been studies that advised against the initiation of statin therapy in cardioembolic stroke patients unless additional cardiovascular indications were present [32].

Therefore, this review evaluated the literature on the role of statins in patients with cardioembolic stroke.

In a 2014 study, statin treatment was reported not to affect the incidence of recurrent stroke in patients with cardioembolic stroke. Choi and colleagues had assessed the effects of statin treatment on mortality and stroke recurrence after cardioembolic stroke. Data was evaluated from 535 patients with first cardioembolic stroke. Statins were associated with reduced mortality. Treatment with statins was shown to have an independent association with reduced mortality (hazard ratio, 0.237; 95% confidence interval, 0.080–0.703 for nonstatin versus low-potency statin; hazard ratio, 0.158; 95% confidence interval, 0.037–0.686 for nonstatinversus high-potency statin). However, statin therapy had no effect on the incidence of recurrent stroke [29].

Table 2: Statins for secondary prevention of ischemic stroke.

Study	Patients	Findings
Tramacere et al, 2019 Systematic review and network meta-analysis [20]	Patients with ischemic stroke or transient ischemic attack	Statins were associated with a reduced risk of ischemic stroke, ischemic stroke or TIA, as well as a cardiovascular event Use of statins was safe
Kitagawa et al, 2017 Randomized open-label trial [22]	Patients with non-cardiogenic ischemic stroke	Statins led to a significant reduction in hs-CRP levels after 2 months; Statins may reduce vascular inflammation as evidenced by hs-CRP
Vitturi et al, 2020 Prospective cohort study [23]	Patients with ischemic stroke	Patients without statins had increased risk of stroke recurrence and worse functional outcomes There was evidence of beneficial role of statins in cases of large-artery atherosclerosis, small-vessel occlusion, and stroke of undetermined cause Patients with poor adherence to statins or discontinuation of therapy had worse prognosis after stroke; early onset of statin use led to better outcomes
NíChróinín et al, 2011 Population-based prospective cohort study [25]	Ischemic stroke patients	Statin therapy at stroke onset and newly initiated statin therapy were associated with improved early and late outcomes New poststroke statin therapy was independently tied to improved early and late survival compared with statin untreated patients: OR for death 0.12 at 7 days; OR 0.19 at 90 days; OR 0.26 at 1 year Similar results for statin therapy before stroke onset

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Around the same time, Ntaios et al, in a long-term registry of patients with AF-related stroke, noted that statin treatment improved survival and decreased the risk for later cardiovascular events. Consecutive patients from the Athens Stroke Registry with AF-related stroke without a prior history of coronary artery disease or clinically manifest peripheral artery disease were part of the analysis. Participants were segregated in two groups based on whether statin was prescribed at discharge of 1602 stroke patients, 404 with AF-related stroke were included in the analysis. Of these, about 25.2% were discharged on statin. Multivariate Cox-proportional-hazards model revealed that statin therapy had an independent association with reduced mortality and a diminished risk for the composite cardiovascular endpoint over a median follow-up of 22 months,but not with stroke recurrence [33].

A relatively recent study by Ko and colleagues evaluated the effect of pre-stroke statin use on functional outcome in AF and noted that statin use at time of stroke onset among these patients was associated with less severe stroke. Pre-stroke statin use was tied to a 32% reduction in frequency of severe stroke. So, statin use at the time of stroke onset among patients with AF was shown to be linked to less severe stroke in this study [34].

Another study has shown the benefit of pre-stroke statin use [32]. Kotlęga and colleagues assessed the effects of pre-stroke statin use on in-hospital outcomes and mortality in cardioembolic stroke patients. The study recruited ischemic stroke patients with AF. Group I (n=181) included patients who had been treated with statins directly prior to the stroke. Group II (n = 153) was the non-statin group. Patients in the non-statin group demonstrated greater initial and discharge NIHSS scores. Statin group had a greater improvement in NIHSS score. Additionally, in-hospital mortality was more frequently reported in the non-statin group. So, despite the fact that statins are predominantly used in atherothrombotic stroke patients, this study revealed the benefits of statins in cardioembolic stroke patients [32].

Another recent study looked into the effect of statin therapy for theprevention of the major vascular events in patients with acutecardioembolic stroke without any other known indication for statin therapy. Among 2,888 patients with cardioembolic stroke, 64.5% were on statin therapy while hospitalized. Following a median follow-up of 359 days, patients given statin therapy had cumulative incidences of major vascular events (a composite of stroke recurrence, myocardial infarction, and vascular death) of 9.3% compared to 20.5% among those not given statins. The adjusted hazard ratios of statin therapy for major vascular events, stroke recurrence, vascular death, and all-cause death were 0.39, 0.81, 0.28 and 0.53, respectively. The study thus revealed that statin therapy could potentially diminish the risks of major vascular events, vascular death, and all-cause death in patients with acute cardioembolic stroke with no clearindication for statin therapy based on current guidance [35].

An exploratory subanalysis of the THRombolysis and Statins (THRaST) study, among 701 patients diagnosed with cardioembolic stroke at discharge, revealed that statin use in the acute phase was tied to neurological improvement, major neurological improvement, favorable functional outcome, and a decreased risk of neurological decline and death. The study reinstated the role of statins within 72 h after IV thrombolysis [36].

Vitturi and Gagliardi recently demonstrated that in patients with cardioembolic stroke, statin use may be beneficial in some cases. Patients in the study were divided into non-statin, simvastatin 20 mg, simvastatin 40 mg, and high-intensity statin (atorvastatin 40 mg or rosuvastatin 10 mg) groups. It was noted that statin therapy may prevent stroke recurrence and improve functional outcomes in these patients. There were 27 cases of stroke recurrence in the study (6 from the nonstatin group, 11 from simvastatin 20 mg group, 6 from simvastatin 40 mg group and 4 from the high-potency group) during follow-up [37].

Statin use, therefore, has beneficial effects in cardioembolic stroke patients, both as pre-stroke therapy and post-stroke intervention. It can be stated that statins may act as effective adjuvant therapy to improve the efficacy of thrombolytic therapy, on account of theirprofibrinolytic and antithrombotic effects [36]. The use of statin treatment after a cardioembolic stroke should be further explored in randomized clinical trials [37].

Table 3 summarizes the findings from the articles included in the review on the role of statins in cardioembolic stroke.

Intensive statin therapy and CVA

Intensive lipid-lowering therapy using statins is recommended following a TIA or an ischemic stroke of atherosclerotic origin. The recommendation is based on the findings from the SPARCL trial showing a lower incidence of recurrent stroke by 16% with atorvastatin 80 mg per day, compared to placebo in patients with stroke and no proven coronary heart disease. The American Heart Association and the American Stroke Association also advocate intensive statin therapy after an ischemic stroke of atherosclerotic origin [38].

Ischemic stroke recurrence has usually been reported within 1 week of a minor stroke. Therefore, there is a particular significance of early active treatment after ischemic stroke [39].

Intensive statin therapy has been shown to reduce the occurrence of microemboli and inflammation in patients with acute ischemic stroke [39]. Chen and colleagues conducted a study among patients with acute ischemic stroke who were randomized to either intensive statin therapy or control treatment within 72 hours of onset. They noted that 58.3% patients had microemboli in the intensive statin group compared to 52.6% in the control group on day 1. On day 3, 15% patient's had microemboli in the intensive statin group compared with 28.1% of controls. Metalloproteinase-9 (MMP-9), hs-CRP, and NIHSS score were also evaluated on days 1 and 7. On day 7, MMP-9 and hs-CRP levels were lower in the intensive statin group compared to control group. There appeared to be no overt adverse events and the liver function of the included patients was not impacted. The study made a strong suggestion that intensive statin therapy could be safely used in patients with acute ischemic stroke [39].

Vitturi and Gagliardi assessed the effects of statins on the neurological outcomes in patients following a cardioembolic stroke. Simvastatin 40 mg treatment was tied to a significantly lower

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Table 3: Role of statins in cardioembolic stroke.

Study	Patients	Findings
Choi et al, 2014 [29]	Patients with first cardioembolic stroke	Treatment with statins was shown to have an independent association with reduced mortality (hazard ratio, 0.237 for nonstatin versus low-potency statin; hazard ratio, 0.158 for nonstatin versus high-potency statin)
Kotlęga et al, 2019 Hospital-based retrospective analysis [32]	Ischemic stroke patients with atrial fibrillation	Patients not treated with statins in the previous year demonstrated greater initial and discharge NIHSS scores (10 vs. 11.9) Patients treated with statins had a greater improvement in NIHSS score (73.5% vs. 59.5%) In-hospital mortality was more frequently reported in the non-statin group (9.9% vs. 18.3%)
Ntaios et al, 2014 [33]	Patients in the Athens Stroke Registry with AF-related stroke, no history of coronary artery disease or clinically manifest peripheral artery disease	Statin therapy had an independent association with reduced mortality (hazard-ratio (HR): 0.49) and a diminished risk for the composite cardiovascular endpoint over a median follow-up of 22 months (HR: 0.44), but not with stroke recurrence (HR: 0.47)
Ko et al, 2017 Cohort study [34]	Patients with ischemic stroke with AF	Prestroke statin use was associated with a 32% reduction in frequency of severe stroke (OR 0.68) at 30 days
Park et, 2020 Retrospective observational study [35]	Patients with acute cardioembolic stroke	Patients given statin treatment had cumulative incidences of major vascular events of 9.3% vs. 20.5% among those not given statins after a median follow-up of 359 days Adjusted hazard ratios of statin therapy for major vascular events, stroke recurrence, vascular death, and all-cause death were 0.39, 0.81, 0.28 and 0.53, respectively
Cappellari et al, 2015 Exploratory subanalysis of the THRaST study [36]	Patients diagnosed with cardioembolic stroke at discharge	Satin use in the acute phase was tied to neurological improvement (OR 2·33), major neurological improvement (OR 1·70), favorable functional outcome (OR 1.87), and a decreased risk of neurological decline (OR 0·18) and death (OR 0·33)
Vitturi and Gagliardi, 2020 Prospective cohort study [37]	Patients with cardioembolic stroke	Statin use may be beneficial in some cases. It may prevent stroke recurrence and improve functional outcomes in these patients Patients receiving 40 mg statin had lower risk of having another stroke during the 2-year follow-up (OR = 0.28)

incidence of stroke recurrence in comparison with simvastatin 20 mg and statin non-use. Simvastatin 40 mg and high-potency statins were associated with the best functional recovery [37].

While intensive statin therapy is recommended following an ischemic stroke of atherosclerotic origin, the ideal LDL target level is not known. So, investigators in the Treat Stroke to Target trial, investigated the hypothesis that a target LDL-C of <70 mg/dL would be superior to a 90-110 mg/dL in reducing overall cardiovascular events after an ischemic stroke or a TIA in patients with atherosclerosis. In the randomized, parallel-group study in France and South Korea, patients with ischemic stroke in the previous 3 months or a TIA within the previous 15 days were randomized to a target LDL-C level of <70 mg/dL(lower-target group) or to a target range of 90-110 mg/dL(higher-target group). The composite primary end point of major cardiovascular events, which included ischemic stroke, myocardial infarction, new symptoms leading to urgent coronary or carotid revascularization, or death from cardiovascular causes, was evident in 8.5% patients in the lower-target group compared to 10.9% in the higher-target group (adjusted hazard ratio, 0.78; 95% confidence interval, 0.61 to 0.98; P=0.04). It was noted that patients with LDL-C target of <70 mg/dLwith the use of statins and, if needed, ezetimibe, had a lower risk of subsequent cardiovascular events compared to those who had a target range of 90-110 mg/dL [38].

The study by Chan et al, mentioned in a previous section in this article, also suggested that among patients at high risk of cardiovascular events, intensive lipid lowering with statin therapy to LDL-C level <2.1 mmol/l significantly decreased the risk of stroke, major coronary events and CVD or CHD deaths, in comparison with LDL-C level ≥ 2.1 mmol/l.17

Data also suggest that perioperative intensive statin treatment in patients undergoing stent implantation for ischemic stroke can also improve patient outcomes [40]. A study evaluating intensive statin therapy during perioperative period in patients undergoing middle cerebral artery (MCA) stent implantation for ischemic stroke evaluated serum levels of CRP, vascular cell adhesion molecule-1 (VCAM-1), and soluble extracellular matrix metalloproteinase inducer (EMMPRIN/CD147) at 24 h before and 24 h after the intervention. The study revealed that the primary end point [procedure-related intra-stent thrombosis, 1-month incidence of major adverse cerebrovascular events (stroke, transient ischemic attack, in-stent restenosis, death or unplanned revascularization)] occurred less often in intensive therapy group compared to the standard therapy group. Perioperative intensive statin treatment led to improvement in patient outcomes, reduced CRP, VCAM-1 and sCD147 levels, and reduced the incidence of cerebrovascular events [40].

A study by Zhou and colleagues evaluated the efficacy of intensive statin treatment in patients with atherosclerotic intracranial arterial stenosis (AICAS). Investigators assessed changes in serum lipid profiles, degree of stenosis, perfusion-related parameters and occurrence of cerebrovascular events during the study period. Patients were randomized to receive low-dose, standard-dose statin therapy or intensive-dose statin therapy. Fifty-two weeks following treatment, there were significantly better improvements in serum lipid profiles, degree of stenosis, and perfusion-related parameters in the intensive therapy group. The cumulative probability of cerebrovascular events was found to be significantly lower in the intensive treatment group compared to the low-dose therapy group. In terms of serum lipid profile, the intensive therapy group reported the highest reduction

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in total cholesterol (TC) and LDL-C serum levels (2.45 ± 0.98 mmol/l and 2.42 ± 0.72 mmol/l at 52 weeks), and the ratio of LDL-C to high-density lipoprotein cholesterol (HDL-C) (2.09 ± 0.19 at 52 weeks). This group also had the greatest increase in HDL-C levels (0.06 ± 0.23 mmol/l) among the three study groups. Intensive therapy group had median reduction in percentage of stenosis after 26 and 52 weeks of -4.5% and -9.3%, respectively, which was significantly lower than other study groups. In terms of computed tomography perfusion (CTP) parameters, median changes for relative cerebral blood flow (rCBF) and relative cerebral blood volume (rCBV) from baseline to 26 and 52 weeks appeared to be greater in the intensive therapy group and the median change in relative time to bolus peak (rTTP) in this group was significantly lower than other two groups after 52 weeks of therapy. The safety profile of intensive therapy was comparable to that of the other therapies [41].

Available evidence, therefore, indicate that intensive lipid lowering leads to stroke risk reduction in comparison with moderate lipid lowering and has been found to be safe as well. High-intensity statin treatment, therefore, appears to be beneficial for stroke patients.

Table 4 summarizes the findings from the articles included in the review for the role of intensive statin therapy in patients with stroke.

Economic implications of statins for the prevention of CVA

Numerous clinical trials and meta-analyses have shown that statins are beneficial in reducing mortality and cardiovascular morbidity in different populations and risk groups [42]. While in developed countries, the majority of the individuals are insured or governments take care of healthcare expenditure of the people,in developing countries like India, most of the healthcare expenditure is out of the patients' pockets [43]. It, therefore, seems prudent to understand the economic implications of statin use.

A study conducted by Chawan et al noted a wide variation in the cost of different brands of oral hypolipidemic drugs available in India [44]. Greving and colleagues evaluated the cost-effectiveness of low dose statin therapy for primary prevention of vascular disease, and noted that statin treatment was not cost-effective for primary prevention in populations that had a low risk of vascular disease. The study emphasized on the need to improve adherence to statin treatment in order to improve the cost-effectiveness of these drugs for primary prevention. Costs of treatment in this study were segregated into those incurred by the drug, laboratory tests, doctors' visits, and pharmacists' fees. All cost estimates were updated to 2008 with Dutch consumer price indices. Cost-effectiveness analysis was done using a Markov model. Incremental cost-effectiveness ratios were calculated [42]. However, a later study noted that 5 years' primary prevention treatment of middle-aged men with a statin was cost saving. Treatment of even younger, lower risk individuals appeared to be cost-effective. In this study, the investigators assessed the costs and benefits of the first 5 years of treatment with statin over the complete follow-up period of approximately15 years in a cost-utility analysis. The perspective of the National Health Service (NHS) for costs and savings, and health benefits [quality-adjusted life years (QALYs) over the follow-up period of 15 years] for patients were employed [45].

A study conducted in the Netherlands revealed that in spite of nonadherence in actual practice, statin treatment was cost-effective

Table 4: Role of intensive statin therapy in stroke.

Vitturi and Gagliardi, 2020 Prospective cohort study [37]	Patients with cardioembolic stroke	Over 2-year follow-up, patients receiving simvastatin 40 mg and high-potency statins had the best functional recovery compared to those without statin treatment and those receiving simvastatin 20 mg
Amarenco et al, 2020 Randomized, parallel-group, event-driven trial [38]	Patients with ischemic stroke in the previous 3 months or a TIA within the previous 15 days	Composite primary end point was evident in 8.5% patients in the lower-target group (<70 mg/dL) compared to 10.9% in the higher-target group (90-110 mg/dL) (adjusted hazard ratio, 0.78; 95% confidence interval, 0.61 to 0.98; P=0.04) Patients with LDL-C target of <70 mg/dL had a lower risk of subsequent cardiovascular events
Chen et al, 2018 Preliminary, randomized controlled study [39]	Patients with acute ischemic stroke	15% patients had microemboli in the intensive statin group vs. 28.1% of controls on day 3 (p = 0.002); 10% had microemboli in intensive therapy group vs. 17.5% of controls on day 7 (p = 0.005) MMP-9 (median 79.3 vs. 95.9 μg/L; p = 0.004) and hs-CRP (median 2.01 vs. 3.60 mg/L; p = 0.020) levels were lower in the intensive statin group vs. controls on day 7
Gao et al, 2016 Randomized trial [40]	Patients undergoing middle cerebral artery (MCA) stent implantation for ischemic stroke	In intensive statin therapy group during perioperative period, incidence of primary end point was lower compared to the standard therapy group Perioperative intensive statin treatment led to improvement in patient outcomes, reduction in CRP, VCAM-1 and sCD147 levels, and reduced the incidence of cerebrovascular events
Zhou et al, 2014 Randomized, single-blind, parallel-group study [41]	Patients with atherosclerotic intracranial arterial stenosis	Intensive therapy group reported the highest reduction in TC and LDL-C serum levels (−2.42 ± 0.98 mmol/l and 2.40 ± 0.73 mmol/l at 26 weeks, and 2.45 ± 0.98 mmol/l and 2.42 ± 0.72 mmol/l at 52 weeks, respectively), and the ratio of LDL-C to HDL-C (−2.07 ± 0.20 at 26 weeks and 2.09 ± 0.19 at 52 weeks, respectively) It had the greatest increase in HDL-C levels (0.06 ± 0.22 mmol/l at 26 weeks and 0.06 ± 0.23 mmol/l, respectively) Intensive therapy group had median reduction in percentage of stenosis after 26 and 52 weeks of −4.5% and −9.3%, respectively (significantly lower than other study groups) Computed tomography perfusion (CTP) imaging - Median changes for rCBF and rCBV from baseline to 26 and 52 weeks were greater in the intensive therapy group; median change in rTTP in the intensive therapy group was significantly lower than other two groups after 52 weeks The cumulative probability of cerebrovascular events at 52 weeks was significantly lower in intensive therapy group compared to low-dose therapy group; no statistical difference between intensive and standard-dose group

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for primary prevention among newly diagnosed type 2 diabetes mellitus patients. In this study, cost-effectiveness analysis was conducted with the help of a Markov model with a time horizon of 10 years. Investigators ascertained the difference in QALYs between no lipid-regulating treatment and statin treatment [46]. A study from Taiwan suggested that reducing the target LDL-C level to 70 mg/dL among treatment-naïve coronary artery disease patients could prove to be cost-effective. This study also used a Markov cohort state-transition model to build up disease progression, understand the health outcomes, and determine overall estimates of cost and QALY. The direct costs and rate of fatal events were obtained from national claims database. Incremental cost-effectiveness ratio (ICER) per QALYs was calculated, and sensitivity analyses were conducted [47].

While treatment with statins has been shown to be cost-effective in some studies, it could be more cost-effective for lower-risk patients as drug prices decline. Clinicians should be more aggressive in treating low-risk patients, and guidelines must consider recommending therapy for a broader patient population [48].

Conclusion

Statins are a class of drugs with well-known role in reducing the cholesterol levels, thereby decreasing vascular event incidence. Primary and secondary prevention trials have often shown the beneficial effects of statins in the prevention and management of stroke. The pleiotropic benefits of statins, besides their cholesterol-lowering effects, are accountable for their potential beneficial effects in the management of stroke. Statins have been shown to be safe and effective for primary prevention of stroke in several trials, such as the JUPITER and the CTT trials. Pre-stroke and post-stroke statin therapy has both been found to be effective in ischemic stroke andcardioembolic stroke. Though statin treatment needs to be explored further in cardioembolic stroke. Evidence also indicates that intensive statin treatment is beneficial for stroke patients and appears to be a safe option.

While there could be a wide variation in the cost of different brands of lipid lowering drugs, treatment with statins could prove to be more cost-effective if the clinicians aggressively treat low-risk patients, and guidelines consider the therapy for a broader patient population.

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Author's contributions

Aditya Mahamankar (AM): Conception and design, literature search, data extraction of the relevant studies, drafting and critically revising the article, and final approval of the version to be submitted.

Ashutosh Sonawane (AS): Literature search, data extraction of the relevant studies, qualitative assessment of the eligible studies, drafting and critically revising the article, and final approval of the version to be submitted.

Suman Kotwal (SK): Data extraction from the relevant articles, drafting and critically revising the article and final approval of the version to be submitted.

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