Archives of Psychiatry and Psychotherapy, 2026; 2: 70–81

10.12740/APP/218978

The impact of statin therapy on cognitive functioning – current state of knowledge

Karolina Sas, Kamila Tokarczyk, Magdalena Piegza

Abstract:

Statins are widely used drugs in the prevention of atherosclerotic cardiovascular disease, but their pleiotropic effects are of growing interest to researchers. In addition to lowering LDL cholesterol levels, they exhibit anti-inflammatory effects, reduce oxidative stress, and improve endothelial function and vascular tension. At the same time, their effect on cognitive functions remains ambiguous. Some studies indicate potential benefits of statin use in reducing beta-amyloid deposition in the brain, especially in patients with Alzheimer's disease. On the other hand, population data on people without dementia are divergent, and their interpretation is complicated by the diversity of research methodologies and the complexity of the mechanisms of action of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors.

Given the increasing number of people with dementia, including Alzheimer's disease, it is crucial to understand the potential impact of statins on neurocognitive function. This review focuses on the available evidence regarding the impact of statins on cognitive function in both people with and without cognitive impairment. It includes molecular mechanisms discovered from laboratory studies as well as clinical data.

statins; cognitive functions; dementia

INTRODUCTION

Statins are a group of drugs used primarily to prevent atherosclerotic cardiovascular disease, which is the leading cause of death and disability in the United States [1]. The mechanism of action of these drugs is based on the inhibition of 3-hydroxy-3-methylglutarate attached to CoA reductase (HMG-CoA), which limits the rate of cholesterol biosynthesis and reduces the level of low-density lipoprotein cholesterol (LDL-C) and on the regulation of low-density lipoprotein receptor expression. However, increasingly, researchers point to pleiotropic effects of statins, which include reducing inflammation, reducing oxidative stress, improving vascular tone and endothelial function, as well as increasing the risk of rhabdomyolysis and hemorrhagic stroke [2].

In the available literature the impact of these drugs on cognitive functions is not clearly presented, which results in a lack of agreement and a large discrepancy in the opinions of doctors on statin therapy. Preceding phenomenon is illustrated by the results of a study conducted among 1,758 doctors of various specializations from Germany, Japan, the Philippines and Colombia. Only 5% of doctors from Germany were in favor of an increased risk of cognitive impairment as a result of statin therapy, while in other

Karolina Sas[1], Kamila Tokarczyk[1], Magdalena Piegza[2]: [1]Student Science Club, Department of Psychiatry, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice; [2]Department of Psychiatry, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice

countries this opinion was shared by 14-37% of respondents [3]. As can be seen from the abovementioned information, these data are not similar, and the variety of opinions on the effect of statins on neurocognitive functioning may result in excessive caution in their use. Hence the idea to present current knowledge on the effect of statins on this aspect of functioning based on the mechanism of action of the drugs. Exploring this issue could result in the creation of another, new indication for the use of statins in addition to the existing one – prevention of atherosclerosis or establishing a specific contraindication to their use.

Diseases that cause cognitive decline include many medical conditions, in this case vascular diseases and Alzheimer's disease [4,5]. In 2018, Alzheimer's Disease International presented research results that dementia affects about 50 million people worldwide. The projected number of patients in 2050 is expected to be three times that number [4]. The growing awareness of Alzheimer's disease has also led to the identification of a "subjective state of cognitive impairment", where no abnormalities are found in the test results and the patient experiences a subjective decline in intellectual abilities [6]. A significant challenge for researchers in the perspective of future statin treatment strategies will be the possibility of establishing specific determinants of the patient's individual cognitive response to various drugs from this group, which is consistent with the concept of personalized psychiatry. Hence the need for the authors of this study to analyze the effect of specific statins on the neurocognitive functioning of people with cognitive disorders and without these disorders at the beginning. Since, as will be shown below, the results are ambiguous, sometimes divergent and most of the materials used in this study refers to patients with Alzheimer's dementia, adopting a uniform position is not possible and is a constant challenge for the medicine of the future.

Purpose and Method

The aim of this work was to organize the current knowledge on the effect of statin use on cognitive functioning. The review of scientific publications was performed using PubMed, National Institute of Mental Health and Google Scholar. For this purpose, the following phrases were used: 'statin therapy', 'cognitive functions', 'cognitive impairment'', 'executive function', 'visuospatial episodic memory', 'psychomotor speed', 'verbal fluency'.

The material used for the analysis was collected from March 2024 to January 2025. The authors used 33 research papers and 7 scientific reviews to prepare the review. When selecting publications, works that did not directly apply to the analyzed topic were rejected. The work was created based on publications from 2018-2024. Selecting the most up-to-date literature allowed us to determine and describe the latest position on this topic. The figure below presents the method of selecting the literature – Figure 1.

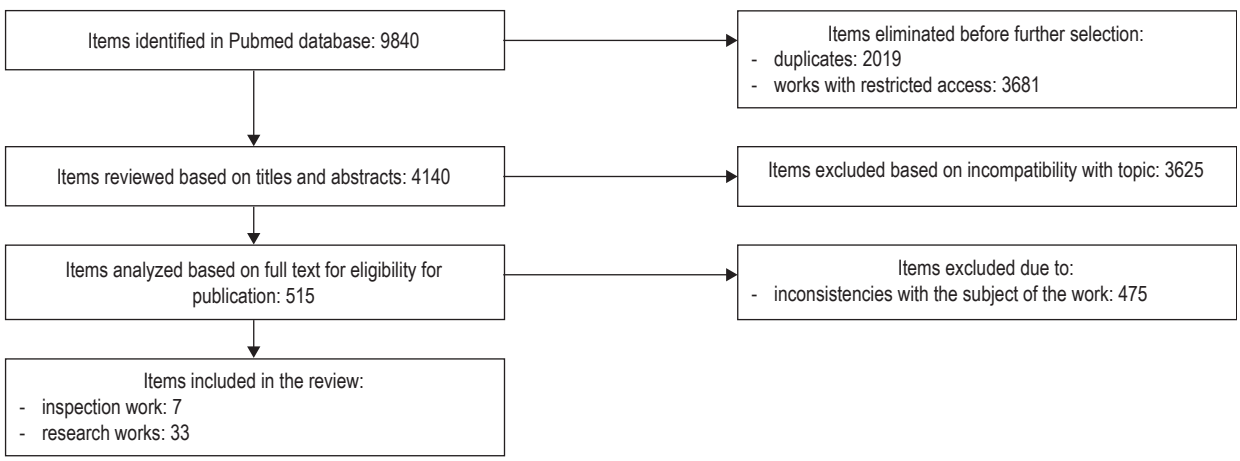

Figure 1. Diagram showing the selection of scientific publications that were included to the narrative review

General information based on the latest data

The American Heart Association (AHA) issued a scientific statement in 2019 regarding the safety of statins and describing the potential side effects of their use. An increased risk of hemorrhagic stroke was observed in people using drugs from this group, while this risk was reduced in people predisposed to stroke caused by cerebral atherosclerosis. In the studies cited by the AHA, no effect on cognitive impairment was observed, which supports the safety of statins in this regard [7]. The data contained in the collective review of publications show that the use of statins in long-term therapy is safe, with a low risk of clinically significant side effects, and the use of drugs from this group does not affect the cognitive functions of patients[8]. These observations were also confirmed in a meta-analysis, which showed a reduced risk of dementia in statin users. It was noted that high cholesterol may increase the risk of Alzheimer's disease at the later age, while statin therapy based on reducing cholesterol levels has a protective effect on the central nervous system (CNS). It has been proven that statins have a pleiotropic effect that induces modulation of pathological biomarkers, therefore slowing down the progression of dementia [9].

Statins are a group of lipid-lowering drugs that have a protective effect on the cardiovascular system. In a population study involving 45,029 patients, the effect of statin use on cognitive functions was assessed. It was noted that each cardiovascular incident significantly increases the risk of cognitive function deterioration. The use of statins over a 5-year period reduced the risk of stroke by 2% in this group, while the risk of heart attack decreased by 2.4%, which slowed down cognitive deterioration [10].

It is worth noting that low density lipoprotein cholesterol (sdLDL-C) and lipoprotein a (Lp[a]) is crucial in the deterioration of cognitive functions assessed by the following tests: delayed word recall, digit symbol substitution (DSST), verbal fluency (WFT) and the overall summary test. It has been observed that a high level of sdLDL-C affectson the deterioration of cognitive functions, while high Lp(a) levels slow down the deterioration of these functions. Greater sensitivity to statins was also observed in patients with high sdLDL-C levels, in whom significant deterioration of neurocognitive functioning was observed. According to the authors of the cited study, this is most likely due to long-term elevated blood cholesterol levels and a predisposition to the deposition of atherosclerotic plaques in the walls of arteries. Despite these data, scientists point to significant cardiovascular benefits associated with the use of statins and the need for further studies [11].

As reported in their review by American scientists who focused on assessing the impact of statins on cognitive impairment as well as determining their protective role in the development of dementia, most studies do not confirm chronic deterioration of cognitive functions associated with statin therapy. However, temporary impairment of cognitive functions during statin therapy was noted among people without dementia. It was also shownprotective effect on the induction of dementia and the development of Alzheimer's disease and improvement of cognitive functions in people with previously confirmed dementia after the use of statin drugs. According to the authors, the pleiotropic effect of statins is associated with the need to identify patients who can derive specific benefits from statin therapy, which forces the adjustment of statin treatment to the needs of patients. Therefore, the physician should determine whether the patient is at risk of cognitive deterioration due to statin therapy or, on the contrary, the use of statins will reduce the risk of cognitive deterioration [12].

Another study conducted in Beijing included 1,062 patients, 677 of whom had been taking statins for at least 6 months. Cognitive function was assessed using MMSE and Montreal Cognitive Assessment (MoCA), to assess memory Auditory Verbal Learning Test (AVLT) was used and to conduct neurological assessment Complement Fixation Test (CFT) and Clock Drawing Test (CDT) were used. Language functions were assessed using the Category Verbal Fluency Test (CVFT). It was noted that the statin group showed better cognitive parameters compared to the control group in each test used [13].

The effect of statin uses on cognitive functions in patients with Alzheimer's dementia

Alzheimer's disease is the leading cause of dementia and cognitive impairment worldwide, resulting from damage to the central nervous system. The exact mechanism of its development is not fully understood, but a characteristic feature of patients is the deposition of beta-amyloidand plaques neurofibrillary tangles in the brain [14]. Due to the widespread use of statin drugs in elderly patients, it seems important to critically reflect on the impact of these drugs on cognitive functioning in the elderly population, in whom normal cognitive functions are often impaired.

In the studies conducted among the population of 18,846 people over 65 years of age, no significant effect of statins on the deterioration of cognitive functions and the induction of dementia was observed. The average incidence of dementia per thousand people in patients taking statins was 6.91, while in people not taking statins – 6.48. This indicator also did not show a significant difference in the induction of dementia in the case of lipophilic statins – 7.14, compared to hydrophilic statins – 6.27. The occurrence of Alzheimer's disease was observed less frequently in people not taking statins compared to those taking them (respectively – 2.65 and 2.97 per 1000 people). However, this difference was not statistically significant. The incidence of Alzheimer's disease was slightly higher in people using lipophilic statins – 3.08, compared to people using hydrophilic statins – 2.71, but these differences were not statistically significant. The deterioration of cognitive functions noticeable at the beginning of statin therapy was not noted in the long-term follow-up, studied for a period of less than 5 years [15]. In turn, the data contained in a systematic review published in 2022 show that the use of statins affects the deterioration of functioncognitive (odds ratio was on average 0.082). A reduction in the area of the cerebral cortex was also observed, as well as an increase in the reaction time of the patient taking statins by about 2.8 mth/year. However, no effect on the induction of dementia was observed, and in most cases the adverse effect of statins was reversible after discontinuation of the drug. The authors of the study drew attention to the cardiovascular benefits of using these drugs, which significantly outweigh the negative impact on cognitive functions. Ultimately, according to the authors of the cited review, the use of statins does not affect the progression of Alzheimer's disease or the induction of dementia with Lewy bodies [16].

In the next analysis, 3 groups of patients were distinguished based on cognitive function assessed before statin treatment: patients with normal cognitive functioning, patients with moderate cognitive impairment and patients with Alzheimer's disease. Memory and executive functions were specifically assessed, along with a global neurocognitive evaluation using the Alzheimer's Disease Assessment Scale (ADAS), providing measures of overall cognitive performance, memory performance, and executive functioning. In this 24-month study, an association was noted between statin use and a slower rate of decline in memory function (memory composite). In addition, statin use had no significant correlation with the time it took for the patient to progress to the next stage of cognitive deterioration in none of the diagnostic groups studied. The remaining study groups did not show any effect of statin use on cognitive functions [17]. The next study was a European, multicenter, randomized phase III clinical trial of nilvadipine (NILVAD), used in people with moderate and mild Alzheimer's disease, which also showed no association between statin use and cognitive decline and no progression of dementia symptoms in elderly people with previously diagnosed Alzheimer's disease. Memory and executive functions were specifically assessed alongside global cognition using validated neuropsychological tests, including the Alzheimer's Disease Assessment Scale–Cognitive Subsection (ADAS-Cog) for overall cognitive performance. The study authors point to the safety and benefits of statin use in terms of preventive action on the cardiovascular system [18].

In view of the many, often inconsistent reports on the association of statins with cognitive functioning in people with Alzheimer's disease and other types of dementia, Nabizadeh et al. conducted their study, in which they observed the effect of beta-amyloid deposition in the brain of statin users. For this purpose, a PET (Positron Emission Tomography) imaging study was per-

formed using 18-fluorodeoxyglucose and [18F] AV45. Initially, no difference in the rate of amyloid deposition was observed in people with dementia taking statins, compared with those not taking drugs from this group. After about 4 years of statin therapy, the increased amyloid deposition was2.0 ± 6.3%, compared to 1.4 ± 4.7% in non-statin treated individuals. Increased amounts of beta-amyloid deposition were observed in patients taking high doses of the drug. It was also noted that the use of statin drugs may slow amyloid deposition in individuals without cognitive impairment [19]. In turn, data obtained from a systematic review of drugs affecting the slowing of the development of Alzheimer's disease and improving cognitive functions confirmed the benefits of using statins. It was noted that statins stimulate the release of an enzyme that breaks down insulin from microglia, which affects the removal of beta amyloid present in extracellular spaces. The level of this enzyme as a result of using statins was higher in the extracellular area, which affected its intensive production, and this in turn affected the degradation of amyloid and the improvement of cognitive functions. In particular, studies in mouse models of Alzheimer's disease, demonstrated that statin treatment reduced intraneuronal oligomeric Aβ levels and led to measurable improvements in memory and learning, as assessed by the Morris water maze and Y-maze tests. These outcomes indicate that statins not only modulate amyloid metabolism but also positively influence spatial memory, working memory, and learning abilities in preclinical models [20].

In the next project, as part of the assessment of the influence of vascular risk factors on biomarkers of Alzheimer's disease and on the conversion rate to dementia in people with mild cognitive impairment (MCI– mild cognitive impairment), the influence of statins on cognitive functions assessed by MMSE and Clinical Dementia Rating (CDR) tests was analyzed. Before statin therapy, high levels of low-density lipoproteins (LDL) and high levels of the amyloid Aβ42 to Aβ40 ratio and tau protein were observed. In the brain MRI image before statin use, extensive degenerative changes in the white matter of the brain were noted, which were reduced after a year of therapy. The beneficial effect of statins on slowing down the progression of dementia in Alzheimer's disease and improving cognitive functions in patients was proven. The results showed a slowdown in the conversion of people with MCI to more severe forms of Alzheimer's disease [21].

Bosch et al. in the international, randomized clinical trial Polycap 3 (TIPS-3) analyzed the effect of a multi-ingredient tablet on cognitive functions in 2098 patients over 65 years of age with intermediate risk of cardiovascular disease. The drug consisted of simvastatin 40 mg and a blood pressure lowering substance (atenolol, hydrochlorothiazideyd and ramipril) and was compared with placebo, or in combination with the aspirin group it was compared with double placebo. Patients qualified for the study were assessed at baseline and at least once during the study with the following tests: MoCA, DSST and the Trial Making Test (TMT). During the 5 years of drug use, deterioration of cognitive functions was observed in 356 patients taking the drug, which was a comparable result to the control group taking placebo (328 patients). According to the authors, the influence on the deterioration of cognitive functions in the study group should be attributed to the action of antihypertensive drugs, not statins. Moreover, no differences were found between the groups in the results of the individual assessment and the development of dementia [22].

Simvastatin, L-arginine and tetrahydrobiopterin are known to affect the endothelial pathway of nitric oxide synthesis. Degrush et al. studied the effect of therapy with these drugs on cerebral blood flow (CBF) in 10 patients with mild Alzheimer's disease or MCI. An increase in CBF of ~13% was noted in the limbic system and ~15% in the cerebral cortex. Cognitive functions were assessed using a battery of standardized tests, including the MMSE for general cognitive status, the ADAS-cog 13 for detailed assessment of memory, attention, language, and orientation, and the CDR and Cognitive Assessment Screening Test (CAST) for functional and cognitive domains. After a 16-week period, the analysis showed significant improvement in cognitive functions assessed using the MMSE scale – from baseline (24.2 ± 3.2) to final (26.0 ± 2.7). In addition, patients with improved results on the ADAS-Cog 13 scale showed a sig-

nificant increase in CBF in the examined brain structures [23].

A group of Polish scientists attempted to systematize knowledge about the effect of statins on interneuronal transmission and to determine neuroprotective mechanisms in the CNS. The authors noted that the first reports of a positive effect of low lipid concentration on the prevention of CNS diseases dates back to the end of the last century. It has been noted that the data on the use of statins in Alzheimer's disease vary, but the vast majority of analyses show a positive or neutral effect of statinsoncognitive functions. These discrepancies were associated with many factors influencing the study, including different degrees of disease advancement, as well as differences in the chemical properties of statins. Lipophilic statins penetrate the blood-brain barrier more easily, causing a stronger effect in the CNS. According to the authors, in order for the studies to be more reliable, they should be well designed and controlled [24].

The effect of statin dose and duration of therapy on cognitive functions

In the following prospective study, the effect of statin doses on cognitive functioning was assessed using a modified version of the MMSE. Cognitive impairment was recorded in the case of obtaining less than 79 points out of 100 possible. 213 patients were divided into two groups, one (66.2% of the examined) was subjected to moderate-intensity statin therapy (MIST), and the other (33.8% of the examined) to high-intensity statin therapy (HIST). An adverse effect of statin use on cognitive functioning was shown in 17.8% of all examined patients, which was 5.7% of those treated with a low dose of the drug (MIST) and 41.7% of those in the group using a high therapeutic dose (HIST). In the HIST group, it was observed that those using atorvastatin compared to rosuvastatin showed a significant deterioration in cognitive functions, i.e. 66.7%, compared to 33.3%, respectively. Also, in the group of patients treated with a low dose of the drug in whom cognitive impairment occurred, 50% of them used atorvastatin, 25% rosuvastatin, and the most beneficial drugs in this context were simvastatin and pravastatin, which were used only in 12.5% of those with diagnosed cognitive impairment. The authors of the study emphasize the relationship between the dose and type of statin used and the quality of cognitive functioning in the patients they studied and the negative correlation between the drug dose and the efficiency of cognitive functions in the global perspective [25]. The authors of another randomized study reached a different conclusion, in which the previously described negative correlation between the drug dose and the quality of neurocognitive functioning was not confirmed. Patients took atorvastatin at a dose of 80 mg/day for 6 months. Cognitive functions were examined using Hopkins Verbal Learning Test-Revised (HVLT-R), Brief Visual Spatial Memory Test-Revised (BVMT-R), which assess verba and visual memory, as well as the Symbol Digit Modalities Test (SDMT), which evaluates attention, processing speed and general cognitive function. However, differences in brain activation patterns were observed, which disappeared after 2 months of drug discontinuation. Increased activity in the striatum was observed in the control group compared to statin-treated patients (test group). Patients treated with statins showed increased bilateral activity in the precuneus during the Figural Memory task (a brain structure located in the medial part of the parietal lobes in the cerebrum), which decreased after drug discontinuation [26].

In a population-based study conducted in the UK, which included 55,114 people, a positive effect of statin use on cognitive function was noted in the elderly group, in whom the reaction time to a cognitive stimulus was shortened, whereas in middle-aged people the reaction time was unchanged. The control group consisted of 245,731 patients. Statin use adversely affected working memory performance in patients regardless of age, but the greatest effect was observed in middle-aged people. The effect of statins on reasoning ability independent of acquired knowledge assessed using the Fluid Intelligence Test was beneficial, as patients achieved better results, especially in the group of middle-aged patients. There was also no connection between the length of statin treatment and the adverse effect on cognitive abilities, i.e. a negative correlation between the duration of treatment and the quality of cognitive functioning. The authors of the

above study noted that the assessment of the effect of statins on neurocognition should take into account the type of drug used, the dose and the age of the patient [27].

In high-risk type 2 diabetes, high-intensity statins are recommended. Unfortunately, this is associated with an increased likelihood of side effects, to which some researchers include cognitive decline. Therefore, in 2020, a study was conducted on 127 patients with type 2 diabetes, who were divided into two groups to determine the optimal doses of statins. The first group received low doses of simvastatin (≤20 mg/day), and the second in high doses of atorvastatin (40 mg/day, and if well tolerated, 80 mg/day). Cognitive functions were studied by means of MoCA and TMT, which evaluates executive function, memory, attention, language, visuospatial ability, abstraction, delayed recall, orientation, and clock-drawing, as well as the Trail Making Test (TMT, part B), which measures attention, visual scanning, psychomotor speed, sequencing, flexibility, and the ability to maintain multiple streams of thought. No significant difference was found between the results of cognitive tests in the first and second groups, and intensification of treatment by switching from a low dose of simvastatin to a much higher dose of atorvastatin did not cause a decrease in cognitive functions assessed in the above tests in patients without previously noted symptoms of dementia. Despite the results obtained, the authors of the described study emphasize the benefits of using statins in high doses over their adverse effects [28]. People with diabetes are predisposed to cognitive decline associated with impaired glycemia. Another study of cognitive function in diabetics found that low-dose statins resulted in modest improvements in cognitive function [29].

A systematic review conducted in 2022 noted that the way statins affect the human body varies depending on the drug used. Statins have many mechanisms of action, which means that each of them works in a different way. However, no relationship was found between the lipophilic nature and the mode of action. Therefore, it is reasonable to consider the effect of statins on cognitive functions individually. According to the authors, the essence is to conduct a study in which the effect of statins on the human body will be analyzed in terms of the dose used, duration of therapy, risk factors for cognitive disorders, genetic factors and comorbidities in a selected group of patients [30].

Simvastatin – studies conducted on mouse models

In chronic hypercholesterolemia models of young mice lacking apolipoprotein E, which is accompanied by moderate hypertension, an increase in the number of pro-inflammatory Ly-6Chi monocytes is observed, while in older mice, increased activity of the immune system facilitates the infiltration of these cells into the brain, which results in memory problems. Memory function in mice improves after the use of simvastatin therapy, which lowers cholesterol levels. The results of the study also indicate an existing relationship between chronic hypercholesterolemia leading to the activation of myeloid cells and inflammation, and memory impairment in older mice [31]. Similar conclusions are presented by other scientists based on studies using atorvastatin [32]. In another study, rats with cognitive impairment, after 3 weeks of simvastatin therapy, showed improved spatial memory and reduced degradation of hippocampal cells, which improved cognitive functions [33].

In turn, in mice with increased expression of transforming growth factor-beta1 (TGF), which causes cerebral hypoperfusion and impaired cerebral vasodilation, cognitive functions deteriorate and dementia occurs after a high-fat diet. The use of simvastatin and physical exercise brings similar, beneficial effects by normalizing endothelium-dependent vasodilatory reactions and limiting inflammation, consequently leading to the prevention or improvement of cognitive impairment observed in the form of better results in object recognition tests. Cognitive function in these studies was evaluated using the Novel Object Recognition (NOR) test, which measures recognition memory by comparing the time mice spend exploring a familiar object versus a novel object, and the Morris Water Maze (MWM), which assesses spatial learning and memory by measuring the latency and efficiency with which mice locate a hidden platform in a water pool. Improvements in these tests reflect enhanced memory retention, learning capacity, and executive function, indicating that

both simvastatin and exercise can mitigate diet-induced cognitive deficits. [34]. Another study conducted on mice with overexpression of TGF also confirms the benefits of simvastatin on cognitive functioning [35].

A significant effect on granule cell maturation via the Wnt/beta-catenin signaling pathway was demonstrated by Xin-Kand Tong et al. Their study on mouse models of Alzheimer's disease (APP) showed that immature neurons in the granule cell layer of the dentate gyrus were characterized by shorter dendrite lengths compared to the wild-type control litter. Importantly, the initial structural changes improved after the use of simvastatin, which did not restore the thickness of the molecular layer, but allowed for obtaining a normalized dendritic length of cell bodies immunostained with doublecortin (DCX), i.e. immature neurons. The basis for cognitive benefits, improvement of spatial memory and granule cell maturation is the activation of the Wnt/beta-catenin pathway by reducing the expression of the endogenous DKK1 protein, as evidenced by the fact that all benefits of the therapy were eliminated after the use of XAV939 – a blocker of the aforementioned pathway [36].

Atorvastatin

Neurological disability is often caused by severe hypoxia caused by global cerebral ischemia. The potential neuroprotective effect of atorvastatin in the above situation was examined in experiments analyzing acute and chronic – 4-week treatment. In the group receiving atorvastatin, the number of degenerating neurons in the Subi and CA1 regions decreased compared to the group receiving the vehicle (Veh). It was shown that excessive activation of NADPH producing destructive reactive oxygen species is responsible for hippocampal damage resulting from ischemia. Oxidative damage was significantly reduced by atorvastatin treatment, which further indicates its antioxidant effect. It also acts by reducing the possibility of astrocyte and microglia activation, which also causes a reduction in neuronal death. Reduced neovascularization resulting from atorvastatin therapy may be another therapeutic target by limiting the delivery of proinflammatory components to the places affected by damage, what may cause limitation of increasing damage [37].

The effects of atorvastatin studied by monomer consumption, transmission electron microscopy (TEM) data, thioflavin-T (ThT) fluorescence assay, and CD spectroscopy indicate the potential of atorvastatin to modulate Aβ42 aggregation in vitro. It was shown that Ca-free atorvastatin has the potential to improve Aβ42 aggregation, while Ca-bound atorvastatin has the potential to improve Aβ42 aggregation. Calcium does not have this property. Moreover, molecular dynamics simulations proved the importance of increasing the concentration of atorvastatin as a factor necessary to inhibit the conformational transition of Aβ from the α-helical structure to the β-sheet [38].

The effect of atorvastatin on cognitive impairment induced by cerebral microhaematomas was studied by Bergeron et al. using mice that were divided according to sex. In male models, atorvastatin therapy resulted in improved visual memory, increased expression of brain-derived neurotrophic factor (BDNF) in the cortex, as well as its receptor – neurotrophic tyrosine kinase receptor 2 (trkB). It induced local modulation of the microglial response to microhaematomas and increased the level of vascular endothelial growth factor (vascular endothelial growth factor, VEGF). An increase in glucose metabolism and modulation of astrocyte morphology in the hippocampus was also observed. In turn, female models were not characterized by modulation of visuospatial memory. Only an increase in BDNF was observed, but without changes in the level of its receptor, and there was a decrease in the expression of cortical estrogen receptors – ERα and ERβ. In both sexes, no effect of pharmacotherapy on body weight and serum cholesterol levels was noted [39]. BDNF has neuroprotective effects by binding to a specific trkB receptor. It may also regulate synaptic interactions that affect memory and cognitive function [40].

Scientists from Seoul and Boston have created a mathematical model examining the effect of atorvastatin on improving cognitive functions in cancer patients taking trastuzumab. The authors of the paper emphasize that recent studies report that atorvastatin in studies on mice shows a reduction in the progression of cognitive disorders at the cellular level. The result of

the study is the beneficial effect of atorvastatin on the patient's cognitive functions. It was noted that high doses of atorvastatin can lead to an improvement in cognitive functions in patients with initial cognitive deterioration. Specifically, atorvastatin appears to support memory, attention, and learning abilities, potentially counteracting the cognitive impairment often associated with long-term cancer therapy. In order to confirm the validity of the mathematical model, a clinical trial should be conducted [41].

Rosuvastatin

According to the latest data, type II diabetes (T2DM) is a cause of increased risk of mild cognitive impairment. The novel proposal of using rosuvastatin (RSV) with vitamin D3 in patients with T2DM showed direct anti-inflammatory effect by increasing the activity of IL27, protective effects by modulating the feedback (crosstalk) between insulin/AKT/GSK-3beta and signaling of the Wnt/Beta-catenin pathway. The results of the study also indicate an increase in the expression of$\alpha 7$ nicotinic acetylcholine receptor($\alpha 7$nAChR), positively influencing Wnt/β-catenin signaling. In addition, RSV treatment improved impaired cognitive functions by reducing cholesterol deposition, Abeta1-42 peptide aggregation, acetylcholinesterase activity, and increasing locomotor activity [42]. Rosuvastatin has also been used in a study of cognitive functions in rats with chronic hypertension. RSV treatment resulted in reduced hypertensive white matter changes, higher expression of tight junction proteins in the corpus callosum and reduced occurrence of deposits Aβ in the cortex and hippocampus. The rats also showed improved cognitive function through better performance in the Morris water maze test and the new object recognition test. These beneficial effects were associated with reduced oxidative stress, improved mitochondrial function, and activation of the Nrf2–ARE pathway, which collectively support neuronal survival and synaptic plasticity, key mechanisms underlying cognition [43].

Lowe's syndrome (LS) is a developmental disease caused by functional deficiencies of the inositol 5-phosphatase Ocrl1, in which cognitive impairment occurs. Statins have previously been shown to inhibit RhoA overactivation, which may be considered as the cause of LS membrane remodeling, by deregulating RhoGTPase signaling. An amelioration of the disease phenotype was observed after high-dose rosuvastatin (100 μM for 1 hour) and lower concentrations (1–10 μM) for prolonged periods (≥72 h), and combined treatment with rapamycin may provide even greater therapeutic benefits [44].

In a study on rats, a high-cholesterol diet was used to induce cognitive impairment, which caused changes in oxidative markers. Rosuvastatin administration improved neurobehavioral performance in rats and improved cognitive function. This proved the effectiveness of the drug in cognitive impairment caused by high blood cholesterol levels in rodents [45].

Lovastatin

The potential use of lovastatin can be seen in the treatment of neurofibromatosis 1, where symptoms include learning disabilities. Randomized, placebo-controlled clinical trial revealed a significant increase in the cortical silence period index included in the cortical inhibition study using TMS protocols during lovastatin therapy. This increase in cortical silent period reflects enhanced GABA_B-mediated inhibition in the motor cortex, suggesting that lovastatin can modulate the excitatory–inhibitory balance in the brain. These physiological changes may underlie improvements in cognitive processes, such as attention, learning, and memory, indicating that lovastatin has the potential to positively influence cognitive function in neurofibromatosis 1 patients. [46].

SUMMARY

In July last year, modified diagnostic criteria for Alzheimer's disease were announced. It is diagnosed based on abnormalities of basic biomarkers assessed in vivo. It should be assumed that people even without clinical symptoms of the disease, i.e. in the preclinical phase but with abnormal biomarkers should be considered ill. In light of these reports, as well as the constantly increasing number of people with symptoms

of dementia and in the era of the development of drugs that act causally in Alzheimer's disease (lecanemab), the potential impact of other drugs on cognitive functioning should not be underestimated. Such drugs include statins, whose action is described as pleiotropic. The reports to date, in the vast majority, show a positive effect of statin use on improving cognitive functions in people affected by Alzheimer's disease, resulting from reduced deposition of beta-amyloid in the brain, which was proven in a PET imaging study.

Recent reports from population studies on the effect of statin therapy on cognitive functioning in individuals without cognitive impairment and without dementia are inconsistent. However, it should be remembered that the most important indication for the use of statins is the prevention of cardiovascular events and the reduction of clinically significant side effects of these incidents, which include impaired cognitive functions caused by stroke. The American Heart Association has confirmed the safety of long-term statin treatment in the context of cognitive functioning. Studies conducted using animal models report on further mechanisms of statin action through their effect on the endothelium of cerebral blood vessels and even the structure of neurons, which may explain their beneficial effect on cognitive functioning. The discrepancy in research results, in addition to the diverse methodology of assessing individual domains of cognitive functions and different statin dosages may be caused by the above-described pleiotropic, difficult to predict effects of drugs that are not fully understood.

Author contribution

Karolina P. Sas, Kamila Tokarczyk contributed equally to this work. All authors were involved in the study conception, data analysis, manuscript preparation, and approved the final version of the manuscript.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation. 2022;145(8):e153-e639.
2. German CA, Liao JK. Understanding the molecular mechanisms of statin pleiotropic effects. Arch Toxicol. 2023;97(6):1529-1545.
3. Barter PJ, Yamashita S, Laufs U, et al. Gaps in beliefs and practice in dyslipidaemia management in Japan, Germany, Colombia and the Philippines: insights from a web-based physician survey. Lipids Health Dis. 2020;19(1):131.
4. Website. https://www.alzint.org/u/WorldAlzheimerReport2018.pdf
5. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. Lancet. 2021;397(10284):1577-1590.
6. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. Lancet Neurol. 2020;19(3):271-278.
7. Newman CB, Preiss D, Tobert JA, et al. Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2019;39(2):e38-e81.
8. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: perception vs. the evidence – focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J. 2018;39(27):2526-2539.
9. Zhu XC, Dai WZ, Ma T. Overview the effect of statin therapy on dementia risk, cognitive changes and its pathologic change: a systematic review and meta-analysis. Ann Transl Med. 2018;6(22):435.
10. Offer A, Arnold M, Clarke R, et al. Assessment of Vascular Event Prevention and Cognitive Function Among Older Adults With Preexisting Vascular Disease or Diabetes: A Secondary Analysis of 3 Randomized Clinical Trials. JAMA Netw Open. 2019;2(3):e190223.
11. Pokharel Y, Mouhanna F, Nambi V, et al. ApoB, small-dense LDL-C, Lp(a), LpPLA activity, and cognitive change. Neurology. 2019;92(22):e2580-e2593.
12. Schultz BG, Patten DK, Berlau DJ. The role of statins in both cognitive impairment and protection against dementia: a tale of two mechanisms. Transl Neurodegener. 2018;7:5.
13. Wang W, Li X. Cognitive function in dyslipidemia patients: exploring the impact of statins. Front Neurol. 2024;15:1436010.
14. Alterations in cholesterol metabolism as a risk factor for developing Alzheimer's disease: Potential novel targets for treatment. J Steroid Biochem Mol Biol. 2019;190:104-114.
15. Zhou Z, Ryan J, Ernst ME, et al. Effect of Statin Therapy on Cognitive Decline and Incident Dementia in Older Adults. J Am Coll Cardiol. 2021;77(25):3145-3156.
16. Rosoff DB, Bell AS, Jung J, Wagner J, Mavromatis LA, Lohoff FW. Mendelian Randomization Study of PCSK9 and HMG-

CoA Reductase Inhibition and Cognitive Function. J Am Coll Cardiol. 2022;80(7):653-662.

17. Kemp EC, Ebner MK, Ramanan S, et al. Statin Use and Risk of Cognitive Decline in the ADNI Cohort. Am J Geriatr Psychiatry. 2020;28(5):507-517.
18. Murphy C, Dyer AH, Lawlor B, Kennelly SP, NILVAD study group. What is the impact of ongoing statin use on cognitive decline and dementia progression in older adults with mild-moderate Alzheimer disease? PLoS One. 2023;18(5):e0285529.
19. Nabizadeh F, Valizadeh P, Balabandian M, Alzheimer's disease Neuroimaging Initiative (ADNI). Does statin use affect amyloid beta deposition and brain metabolism? CNS Neurosci Ther. 2023;29(5):1434-1443.
20. Behl T, Kaur I, Fratila O, Brata R, Bungau S. Exploring the Potential of Therapeutic Agents Targeted towards Mitigating the Events Associated with Amyloid-β Cascade in Alzheimer's Disease. Int J Mol Sci. 2020;21(20). doi:10.3390/ijms21207443
21. Cheng YW, Chiu MJ, Chen YF, Cheng TW, Lai YM, Chen TF. The contribution of vascular risk factors in neurodegenerative disorders: from mild cognitive impairment to Alzheimer's disease. Alzheimers Res Ther. 2020;12(1):91.
22. Bosch JJ, O'Donnell MJ, Gao P, et al. Effects of a Polypill, Aspirin, and the Combination of Both on Cognitive and Functional Outcomes: A Randomized Clinical Trial. JAMA Neurol. 2023;80(3):251-259.
23. Degrush E, Shazeeb MS, Drachman D, et al. Cumulative effect of simvastatin, L-arginine, and tetrahydrobiopterin on cerebral blood flow and cognitive function in Alzheimer's disease. Alzheimers Res Ther. 2022;14(1):134.
24. Kosowski M, Smolarczyk-Kosowska J, Hachuła M, et al. The Effects of Statins on Neurotransmission and Their Neuroprotective Role in Neurological and Psychiatric Disorders. Molecules. 2021;26(10). doi:10.3390/molecules26102838
25. Roy S, Hyman D, Ayyala S, et al. Cognitive Function Assessment in Patients on Moderate – or High-Intensity Statin Therapy. J Clin Med Res. 2020;12(4):255-265.
26. Taylor BA, Dager AD, Panza GA, et al. The effect of high-dose atorvastatin on neural activity and cognitive function. Am Heart J. 2018;197:166-174.
27. Alsehli AM, Olivo G, Clemensson LE, Williams MJ, Schiöth HB. The Cognitive Effects of Statins are Modified by Age. Sci Rep. 2020;10(1):6187.
28. Thongtang N, Tangkittikasem N, Samaithongcharoen K, Piyapromdee J, Srinonprasert V, Sriussadaporn S. Effect of Switching from Low-Dose Simvastatin to High-Dose Atorvastatin on Glucose Homeostasis and Cognitive Function in Type 2 Diabetes. Vasc Health Risk Manag. 2020;16:367-377.
29. Luchsinger JA, Younes N, Manly JJ, et al. Association of Glycemia, Lipids, and Blood Pressure With Cognitive Performance in People With Type 2 Diabetes in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care. 2021;44(10):2286-2292.
30. Jamshidnejad-Tosaramandani T, Kashanian S, Al-Sabri MH, et al. Statins and cognition: Modifying factors and possible underlying mechanisms. Front Aging Neurosci. 2022;14:968039.
31. Don-Doncow N, Vanherle L, Matthes F, et al. Simvastatin therapy attenuates memory deficits that associate with brain monocyte infiltration in chronic hypercholesterolemia. NPJ Aging Mech Dis. 2021;7(1):19.
32. Gong F, Shi Q, Mou X, Wang K, Wang Q, Wang H. Atorvastatin mitigates memory deficits and brain monocyte infiltration in chronic hypercholesterolemia. Aging. 2023;15(23):13669-13679.
33. Adeli S, Zahmatkesh M, Ansari Dezfouli M. Simvastatin Attenuates Hippocampal MMP-9 Expression in the Streptozotocin-Induced Cognitive Impairment. Iran Biomed J. 2019;23(4):262-271.
34. Trigiani LJ, Royea J, Tong XK, Hamel E. Comparative benefits of simvastatin and exercise in a mouse model of vascular cognitive impairment and dementia. FASEB J. 2019;33(12):13280-13293.
35. Tong XK, Trigiani LJ, Hamel E. High cholesterol triggers white matter alterations and cognitive deficits in a mouse model of cerebrovascular disease: benefits of simvastatin. Cell Death Dis. 2019;10(2):89.
36. Tong XK, Royea J, Hamel E. Simvastatin rescues memory and granule cell maturation through the Wnt/β-catenin signaling pathway in a mouse model of Alzheimer's disease. Cell Death Dis. 2022;13(4):325.
37. Kho AR, Hong DK, Kang BS, et al. The Effects of Atorvastatin on Global Cerebral Ischemia-Induced Neuronal Death. Int J Mol Sci. 2021;22(9). doi:10.3390/ijms22094385
38. Nedaei H, Rezaei-Ghaleh N, Giller K, et al. The calcium-free form of atorvastatin inhibits amyloid-β(1-42) aggregation in vitro. J Biol Chem. 2022;298(3):101662.
39. Bergeron S, Barus R, Leboullenger C, et al. Beneficial effects of atorvastatin on sex-specific cognitive impairment induced by a cerebral microhaemorrhage in mice. Br J Pharmacol. 2021;178(7):1705-1721.
40. Ahmed MA, Kamel EO. Involvement of H S, NO and BDNF-TrkB signalling pathway in the protective effects of simvastatin against pentylenetetrazole-induced kindling and cognitive impairments in mice. Basic Clin Pharmacol Toxicol. 2020;127(6):461-476.
41. Lee J, Kim JS, Kim Y. Atorvastatin-mediated rescue of cancer-related cognitive changes in combined anticancer therapies. PLoS Comput Biol. 2021;17(10):e1009457.
42. Muneeb M, Mansou SM, Saleh S, Mohammed RA. Vitamin D and rosuvastatin alleviate type-II diabetes-induced cognitive dysfunction by modulating neuroinflammation and ca-

nonical/noncanonical Wnt/β-catenin signaling. PLoS One. 2022;17(11):e0277457.

43. Zheng L, Cai Y, Qiu B, Lan L, Lin J, Fan Y. Rosuvastatin Improves Cognitive Function of Chronic Hypertensive Rats by Attenuating White Matter Lesions and Beta-Amyloid Deposits. Biomed Res Int. 2020;2020:4864017.
44. Madhivanan K, Ramadesikan S, Hsieh WC, et al. Lowe syndrome patient cells display mTOR – and RhoGTPase-dependent phenotypes alleviated by rapamycin and statins. Hum Mol Genet. 2020;29(10):1700-1715.
45. Husain I, Akhtar M, Madaan T, Abdin MZ, Islamuddin M, Najmi AK. Rosuvastatin alleviates high-salt and cholesterol diet-induced cognitive impairment in rats via Nrf2-ARE pathway. Redox Rep. 2018;23(1):168-179.
46. Bernardino I, Dionísio A, Castelo-Branco M. Cortical inhibition in neurofibromatosis type 1 is modulated by lovastatin, as demonstrated by a randomized, triple-blind, placebo-controlled clinical trial. Sci Rep. 2022;12(1):13814.