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Review Article

Do statins prevent Alzheimer's disease? A narrative review☆

Homayoun L. Daneschvar [a,*], Mark D. Aronson [b,1], Gerald W. Smetana [b]

[a] Harvard Medical School, Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center/Shapiro 621C, 330 Brookline Ave, Boston, MA 02215, United States
[b] Harvard Medical School, Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, MA, United States

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ABSTRACT

Alzheimer's disease is the most common cause of dementia and occurs commonly in patients 65 and older. There is an urgent need to find an effective management that could help prevent or at least slow down the progress of this major public health problem. Cholesterol related pathways might play a role in the pathogenesis of Alzheimer's disease. Treatment with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) has been suggested to promote the prevention of Alzheimer's disease. In this review, we discuss potential pathogenetic pathways for the development of Alzheimer's disease and review the evidence regarding the value of statins as a strategy to prevent or delay progression of Alzheimer's disease.

It has been suggested that vascular and cholesterol-related pathways might play a role in the development and pathogenesis of Alzheimer's disease (AD) and vascular dementia [1,2]. Therefore, several studies have examined possible benefits of statins in preventing or reducing the risk of AD and dementia. In 2012, the United States Food and Drug Administration (FDA) has warned about possible negative effect of statins on cognitive function [3]. In subsequent literature, it was concluded that statins do not show any increased risk of cognitive decline [4].

Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are unequivocally beneficial in preventing coronary heart disease events in high-risk primary and all secondary prevention populations. This beneficial effect of statins is thought to be related both to their ability to reduce low density lipoprotein (LDL) [5–7] and other pharmacological benefits, such as anti-inflammatory, antioxidant, and neuro-protective effects [8].

Statins are categorized based on the solubility, origin and their activity. Statins are divided into two different subclasses according to their solubility: lipophilic and hydrophilic. Lovastatin, simvastatin, atorvastatin, fluvastatin and pitavastatin are lipophilic. Rosuvastatin and pravastatin are hydrophilic. Synthetic statins are atorvastatin, cerivastatin, fluvastatin, pitavastatin, and rosuvastatin. Simvastatin, lovastatin, mevastatin, and pravastatin are fermentation products of naturally occurring products.

Additionally, there are different ways that each statin can be taken up by the liver, catabolized and excreted. For instance, simvastatin and lovastatin circulate as an inactive prodrug while synthetic statins such as atorvastatin and rosuvastatin are biologically active.

1. Statins and their pleiotropic effects

HMG-CoA reductase inhibitors are the most powerful FDA approved cholesterol lowering medications. They target the liver and inhibit endogenous cholesterol biosynthesis, which leads to deceased intracellular levels of cholesterol in the liver cells, followed by the up-regulation of LDL receptors on the cell surface [9].

Statins have multiple effects far beyond their cholesterol and lipid-lowering properties which may in part explain their effectiveness (Table 1).

Statins enhance blood perfusion by increasing the production of vasodilators, such as prostaglandin I_2 and nitric oxide (NO), and by reducing the production of vasoconstrictors, such as angiotensin II [10,11].

NO, which is produced from L-arginine, is necessary for normal endothelial function. It results in vasodilation and improved vascular permeability [12]; NO also limits inflammation and coagulation [13].

Statins have anti-inflammatory properties; they suppress the release of pro-inflammatory cytokines, chemokines, matrix metalloproteinases (MMPs), and adhesion molecules by inflammatory cells [14]. Statins might be beneficial in reducing the inflammation in atherothrombotic events by action on smooth-muscle function and macrophages [15,16].

Several studies have also demonstrated that statins inhibit platelet function, as assessed by ex vivo tests of platelet aggregation or by analysis of circulating molecules released by platelets on activation, such as soluble CD40L or P-selectin [17,18]. Statins also interfere with activation of the clotting system and the coagulation cascade [19]. These combined

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* Corresponding author. Tel.: +1 617 754 9600; fax: +1 617 667 8665.
E-mail addresses: hdanesch@bidmc.harvard.edu (H.L. Daneschvar), maronson@bidmc.harvard.edu (M.D. Aronson), gsmetana@bidmc.harvard.edu (G.W. Smetana).
[1] Tel.: +1 617 667 3992; fax: +1 617 667 8665.

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Table 1
Pleiotropic effects of statins.

- Cholesterol and lipid lowering activities by lowering cholesterol biosynthesis and up-regulation of LDL receptors
- Enhancing blood perfusion by increasing the production of vasodilators (e.g. prostaglandin I_2 and nitric oxide)
- Anti-inflammatory effects by suppressing the release of pro-inflammatory cytokines, chemokines and matrix metalloproteinases
- Inhibiting platelet aggregation and decreasing the activation of blood coagulation cascade
- Antioxidant effects partially as a result of inhibition of NADPH oxidase
- Plaque stabilization as a result of anti-inflammatory effect of statins

effects may exert a beneficial effect with a mechanism related to statins' antithrombotic properties.

These myriad mechanisms have led to the hypothesis that statins might have a role in preventing Alzheimer's disease [20].

2. Alzheimer's disease

AD is the most common cause of dementia worldwide [21,22]. It occurs mostly in the elderly, and has unclear pathogenesis. The characteristics of AD include deposition of amyloid beta (Aβ) peptide and the neurofibrillary tangle [23], impaired memory, language dysfunction, the inability to recognize items or faces, and loss of ability to perform coordinated acts (dyspraxia) [24,25].

Furthermore, animal models and clinical studies strongly suggest that inflammation contributes to AD pathogenesis [26].

AD is also associated with cerebral hypoperfusion, lower vascular tone, angiogenesis, and deposition of Aβ along arteriolar walls, which leads to blood flow disturbances [27]. Aβ is a neurotoxin and a proteolytic fragment of amyloid precursor protein (APP), which plays a crucial role in pathogenesis of AD.

ApoE is the most common genetic risk factor for late-onset sporadic AD [28]. ApoE is an apo-lipoprotein in the brain that is part of the lipid transport process in the bloodstream and in the cerebrospinal fluid. ApoE4 increases the risk of developing late-onset AD [29,30].

3. Cholesterol metabolism in the central nervous system

An intact blood–brain barrier inhibits the transfer of the cholesterol from periphery into the central nervous system (CNS). The majority of cholesterol needed by the brain is produced inside the CNS. The brain as an organ has one of the highest cholesterol concentrations in the body. The cholesterol molecule plays a major role in the membrane components of neurons and maintenance of their functions [31].

4. Connection between cholesterol level and Alzheimer's disease

It is well established that high serum cholesterol is associated with atherosclerosis and vascular disease [32]. Experiments in vivo and in vitro have also suggested that cholesterol may accelerate the production of the Alzheimer's-related amyloid Aβ [33,34].

Generation and clearance of Aβ are regulated by cholesterol. Elevated cholesterol levels increase Aβ in cellular and most animal models of AD, and cholesterol-lowering medications, such as statins, lower Aβ in this model [35].

5. The effects of statins on patients without Alzheimer's disease

An earlier control study of individuals over aged 50 years had suggested that statins may reduce the development of dementia (Table 2). This effect was independent of serum lipid values, as well as exposure to non-statin lipid-lowering medications. These data did not distinguish between AD and other forms of dementia [36].

The Sacramento Area Latino Study on Aging (SALSA) was a prospective cohort study of 1789 older (≥60 years of age) Mexican American individuals from the Sacramento, CA, area without a previous diagnosis of dementia. Statin users were about half as likely as those who did not use statins to develop dementia/cognitive impairment (HR = 0.52; 95% CI 0.34, 0.80) during a 5-year follow-up period [37]. As this was an observational study, other differences between the two groups may have accounted for some of the observed reduction in new onset cognitive impairment.

The AD Anti-inflammatory Prevention Trial (ADAPT) was a prospective observational study aimed to assess whether statin use was associated with reduced risk of incident AD among ADAPT participants. Elective statin use was associated with significantly reduced risk of incident AD that persisted after adjustment for age, gender, education and apolipoprotein E (ApoE) genotype [38].

The Rotterdam Study is the largest population-based observational study of this kind. It followed 6992 participants for a mean of 9 years. The authors demonstrated that use of statins was associated with a lower risk of AD (hazard ratio 0.57; 95% CI 0.37 to 0.90) compared with those that did not use cholesterol-lowering drugs. The use of non-statin cholesterol-lowering drugs was not found to have the same association. The protective effect was independent of the lipophilicity of statins and ApoE genotype [39].

Table 2
Characteristics of the studies.

	Type of the study	Number of patients	Type of statins	Major outcomes
Swiger KJ et al. 2013	Review and meta-analysis	23,443	Simvastatin, lovastatin, pravastatin,	Long-term data may support beneficial role for statins in the prevention of dementia
Haag MD et al. 2009	Prospective, population-based	6992	Atorvastatin, rosuvastatin, pravastatin, fluvastatin, cerivastatin, simvastatin	Use of statins was associated with a lower risk of AD
McGuinness B et al. 2009	Cochrane systematic review	26,340	Simvastatin, pravastatin	Statins given to older patients at risk for vascular disease were not beneficial in preventing dementia
Cramer C et al. 2008	Population-based cohort study	1789	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	Statin users were about half as likely as those who did not use statins to develop dementia/cognitive impairment
Sparks D et al. 2008	Prospective observational study	2233	Not reported	Elective statin use was associated with significantly reduced risk of AD
Heart Protection Study collaborative 2002	Randomized placebo-controlled trial	20,536	Simvastatin	No significant difference in cognitive function existed between the treatment and placebo group
Shepherd J et al. 2002	Randomized controlled trial	5804	Pravastatin	Significant benefit of pravastatin on the development of cognitive dysfunction
Jick H et al. 2000	Case–control design	60,901	Simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin	Individuals of 50 years and older had substantially lower rate of dementia