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Does statin use cause memory decline in the elderly?

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ABSTRACT

Statin therapy has strong evidence supporting health benefits and mortality reduction in cardiovascular disease, stroke, diabetes, renal disease, and genetic lipid disorders. Further, reports that statin therapy might be protective against Alzheimer's disease have subsequently been refuted in randomized trials. Low-level evidence based on case reports suggests that statins may adversely affect memory, a significant consumer concern. In this review, the published evidence on statins and memory in the elderly in randomized controlled trials and prospective observational cohort studies was examined in detail.

Overall, there was moderate-strength evidence that statin therapy did not increase the risk of dementia in the elderly and low-strength evidence for no increased risk for Alzheimer's disease. Further, there was moderate-strength evidence that statin therapy in the elderly did not increase the risk for mild cognitive impairment or worsen global cognitive performance in the cognitively intact or impaired. There was moderate-strength evidence for no deterioration of memory function in the elderly.

On balance, there was a moderate level of evidence of neither harm nor benefit on memory; however, the published literature contains a number of deficiencies that are detailed in this review, not limited to selection biases and deficiencies of detailed testing.

Key words: Cognition, Memory, Dementia, Statins, HMGCoA reductase inhibitors, Brain, Brain volume, Magnetic resonance, Diabetes, Hypertension, Heart, Ischemic heart disease, Stroke.

> Memory is the treasury and guardian of all things.
> Marcus Tulius Cicero (106-43 BC)

Introduction

A novel experiment in human longevity is being played out. The 20th century precedents of enduring access to food, clean water, and shelter, and advances in immunization, antibiosis, and other aspects of modern medicine have established large human populations into their eighth and ninth decades, even beyond. Maintaining health, vigor, productivity, and quality of life into these elderly years is a major concern and interest, not only for individuals as they age but also for healthcare providers, policy makers, and industry. Central to the maintenance of independent living with high quality of life is good

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cognition and brain health, both strongly reliant on cardiovascular and metabolic health. Maintenance of cognitive function in aging is a very significant concern, given the real fear of dementia in our society [1]. With an increasing interest in preventing dementia, there is considerable research into mild cognitive impairment (MCI) that precedes dementia [2] and subjective cognitive complaints (SCC) that are often present in older people in the absence of objective impairment and may be indicators of vulnerability to future cognitive decline [3]. Rates of progression from MCI to dementia have been estimated to be about 6–10% per year [4].

For obvious reasons, many middle-aged and elderly people place a high priority in maintaining cognitive health. Cardio- and cerebrovascular disease and diabetes are common in the elderly, and each increases the risk of dementia, both vascular dementia and Alzheimer's disease. The estimated relative risk of dementia in diabetes is 1.46 (1.20–1.77) [5] and midlife hypertension 1.60 (1.16–2.24) [5]. Coronary artery disease (CAD) is an independent risk factor for cognitive impairment [6]. Stroke doubles the risk of new-onset dementia, and the prevalence of dementia with multiple strokes is more than 30% [6].

There is a strong evidence supporting health benefits and mortality reduction from the use of hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) therapy in cardiovascular disease, stroke, diabetes, renal disease, and genetic lipid disorders. A series of meta-analyses from the Cholesterol Treatment Trialists Collaboration reported reductions in mortality and incident vascular events [7–9]. Relevant to such statements is consideration of the participants recruited to these studies, their age, sex, and underlying conditions. Further, the meta-analyses also reported that statin-induced LDL reduction was not associated with any greater risk of major adverse health events, specifically incident cancer, cancer, or all-cause mortality [9]. Recent recommendations have expanded the indications and reduced the thresholds for statin prescription [10].

Statins are commonly used to reduce the risk of CAD and stroke, considered to be evidence-based standard-of-care. A logical conclusion would be that statins would be protective for brain health as well. However, memory and/or cognitive changes are the second most frequently reported statin-associated adverse effect [11]. A label warning cautioning that statin medications may be associated with cognitive effects is currently required by the Federal Drugs Administration of the United States, based on the volume of cases reported through its adverse event reporting system [12]. Consumer and clinician interest in this topic is clearly high, given the widespread use of statins and questions regarding potential cognitive adverse effects of lipid-lowering therapy raised by published reports. This review examines the evidence for cognitive and memory decline associated with statin therapy in midlife and the elderly.

Methods

The published literature was examined using PubMed and the search terms statin, memory, and cognition. Selection was limited to longitudinal clinical studies, specifically observational studies and randomized placebo-controlled trials and meta-analyses.

Evidence evaluation

In evaluating the quality of the evidence, particularly in summarizing the findings of the published literature, consideration was given to a number of factors that might mitigate or support the strength of the study findings. These included (i) cohort size, age, and study duration; (ii) the definition of statin exposure (e.g., ever used, use at observation commencement, or continuous use through observation period); (iii) the ascertainment of statin exposure (e.g., self-report, prescription, database, or medication inspection); (iv) the measured outcome (e.g., dementia, memory, or a global cognitive measure; (v) the method used to ascertain dementia or measure memory, or a global cognitive measure; (vi) the definition of controls; (vii) whether important covariates that might affect memory were measured; (viii) the statistical methodology used to analyze the data and whether covariates were included in the analyses; (ix) the proportion of dropouts and how they were handled; and (x) evaluation for selection biases in cohort recruitment and covariate inclusion.

Two substantive factors mitigate against the strength of the evidence in cohort studies that have examined statin use and memory in the elderly. The first is that statin users are more likely to have higher rates of cardiometabolic risk factors that promote memory decline. These can be statistically controlled for as covariates to minimize this bias between controls and statin users. The second challenge is that of dropouts, in that survivor biases may skew results. A statistical strategy of minimizing the biases introduced by healthy survivors and dropouts is linear mixed modeling analysis that is currently recommended for handing longitudinal cohort data. It is noteworthy that its application to epidemiological datasets has been advocated only relatively recently and the majority of published studies did not utilize this statistical method.

Results

The evidence on statins and memory in the elderly: Longitudinal observational cohort studies

Table 1 shows the findings for published prospective cohort studies that included a proportion of subjects aged 70 years or more at baseline. Outcomes are separated into (i) incident dementia, (ii) incident mild cognitive impairment, (iii) global cognition change in participants with intact cognition at baseline, (iv) global cognition change in participants with impaired cognition at baseline, and (v) memory performance change. For each study, Table 1 describes the number of participants recruited, observation duration, sex distribution, the definition of "control" (in terms of past statin exposure), the definition of statin exposure (ever, current, and the minimum exposure duration), the methods used to ascertain the memory outcome, the number of assessments during the observation period, and the covariates measured