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## Q/ Do statins alter the risk or progression of dementia?

### EVIDENCE-BASED ANSWER

**A/ No.** Moderate-intensity statin therapy (with pravastatin or simvastatin) doesn't prevent progression to dementia in patients at increased risk. No prevention studies address high-intensity statin therapy (strength of recommendation [SOR]: **A**, randomized controlled trials [RCTs]).

Neither moderate- nor high-intensity

statin therapy (with simvastatin or atorvastatin, respectively) improves existing mild to moderately severe Alzheimer's or vascular dementia (SOR: **A**, RCTs).

Although statin use is associated with a mild, rare, reversible delirium, it isn't linked to permanent cognitive decline (SOR: **C**, expert opinion).

### Evidence summary

A 2016 Cochrane systematic review identified 2 double-blind RCTs that evaluated statins for preventing cognitive decline and dementia in patients with either risk factors or a history of vascular disease.<sup>1</sup> The authors couldn't perform a meta-analysis because of heterogeneity.

#### Statins don't prevent dementia

The first RCT found that 5804 patients (70-82 years old with pre-existing vascular disease or increased risk because of smoking, hypertension, or diabetes) manifested equivalent cognitive decline at 3.5 years after random assignment to pravastatin 40 mg/d or placebo.<sup>2</sup> Investigators measured cognition with the Mini-Mental State Exam (MMSE), which scores cognitive function on a scale of 0 to 30, with higher numbers indicating better function (mean difference [MD] at follow-up=0.06 points; 95% confidence interval [CI], -0.04 to 0.16).

A second RCT evaluated simvastatin 40 mg/d or placebo for as long as 5 years in 20,536 patients 40 to 80 years of age with a history of coronary artery disease or diabetes.<sup>3</sup> The study excluded patients with dementia at baseline. The odds of developing

dementia didn't differ between groups (odds ratio=1.0; 95% CI, 0.61-1.65).

Both studies were originally designed to measure cardiovascular outcomes. The authors rated both as high quality with a low risk of bias.

#### A contrast to earlier, lower-quality studies

These results contrast with an earlier meta-analysis based on one of the previously described RCTs and lower-quality evidence (16 cohort studies and 3 case-control studies) that found using statins to be associated with lower relative risk (RR) of dementia than not using a statin (all-type dementia RR=0.82; 95% CI, 0.69-0.97; Alzheimer's disease RR=0.70; 95% CI, 0.60-0.83).<sup>3,4</sup>

The total patient population was more than 2 million and varied widely. Duration of statin use and type of statin (simvastatin, atorvastatin, fluvastatin, pravastatin, rosuvastatin) also varied. The authors noted potential bias in results for 2 reasons: Cross-sectional studies included patients with impaired cognition who were less likely to be prescribed statins, and statin use was determined by patient self-report.

## Statins don't treat dementia

A Cochrane review that included 4 RCTs with 1154 patients, 50 to 90 years old, assessed the effect of  $\geq 6$  months of statin therapy (atorvastatin 80 mg/d or simvastatin 40-80 mg/d) on the course of Alzheimer's disease and vascular dementia.<sup>5</sup> Most patients had mild to moderate dementia and most were also taking an anticholinesterase inhibitor.

All studies reported outcomes using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), scored 0 to 70, with lower numbers indicating better function, and the MMSE. Results of statin use were equivalent to placebo (ADAS-Cog MD= -0.26; 95% CI, -1.05 to 0.52; MMSE MD= -0.32; 95% CI, -0.71 to 0.06).

## But do they slow its progression?

In contrast, a case-control study of 6431 patients with mild-to-moderate Alzheimer's disease concluded that statin use was associated with slower progression of AD.<sup>6</sup> Using cholinesterase inhibitor discontinuation as a proxy for worsening dementia, researchers noted that patients with early statin exposure (719 patients) had a lower rate of cholinesterase discontinuation than patients who didn't receive early statin therapy (RR=0.85; 95% CI, 0.76-0.95).

A 2016 systematic review attempted to identify randomized clinical trials evaluating

the effects of statin withdrawal in dementia.<sup>7</sup> None were found.

## Recommendations

Based primarily on post-marketing surveillance data, the US Food and Drug Administration (FDA) has warned that memory loss and confusion are occasionally associated with statin use from within one day to several years of initiation.<sup>8</sup> The FDA indicated that such symptoms are rare, not associated with dementia or clinically significant cognitive decline, and resolve with discontinuation of the medication. **JFP**

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