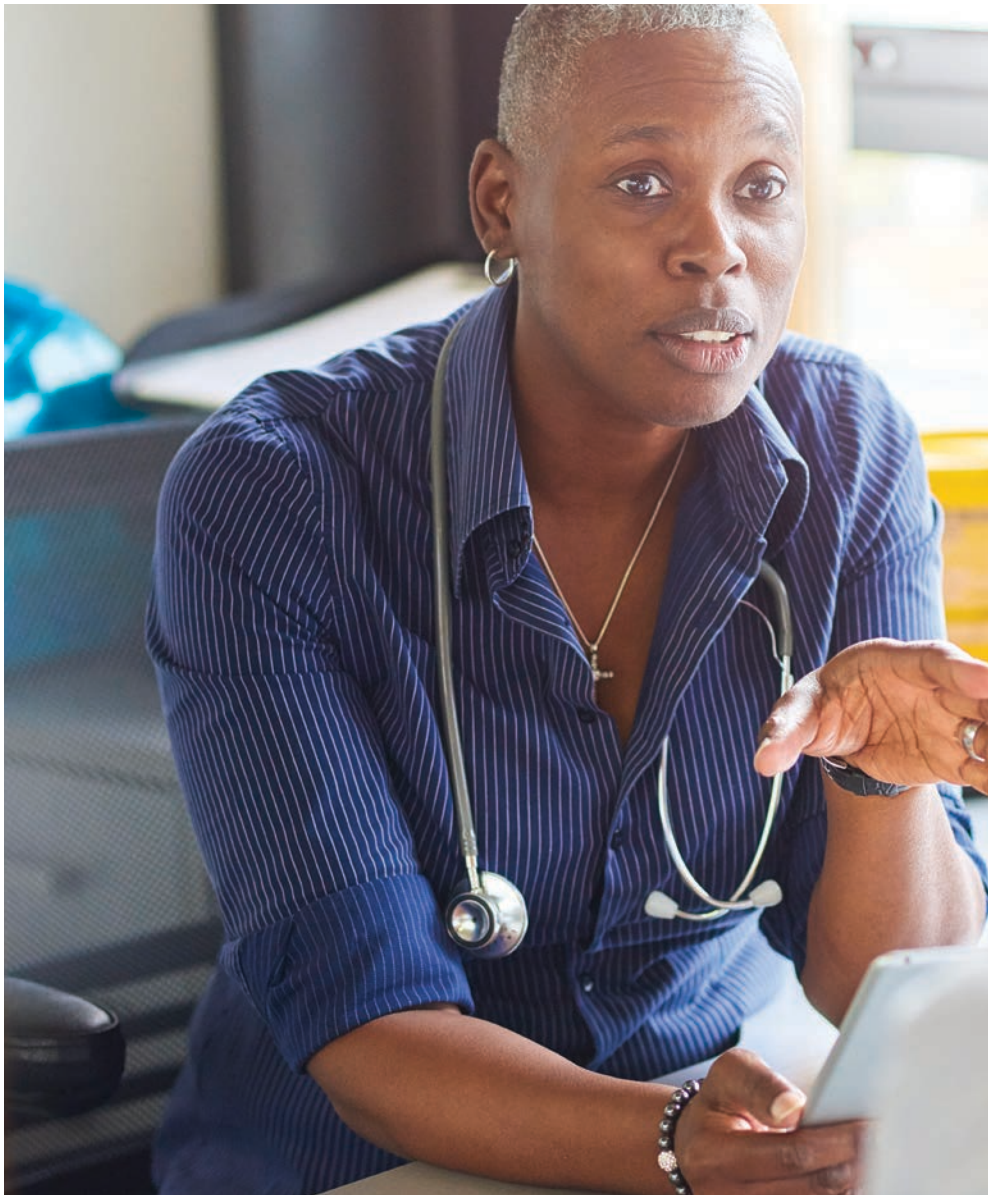
Will statins stave off dementia?

DR MICHAEL TAM
BSC(MED), MBBS, MMH(GP), FRACGP
Senior Lecturer, Discipline of GP, USyd;
Staff Specialist, SWSLHD & Ingham Inst.

It's a question worth asking, especially for patients with a family history of the disease



CLINICAL SCENARIO

Jonathan, a 60-year-old businessman, recently visited for a health check. He was well but raised the challenges of providing care for his father, who had advanced Alzheimer's disease, and mentioned that he read on the internet that statins could be used to prevent dementia. Jonathan wondered whether this was something he should take.

CLINICAL QUESTION

Can statins, used as prophylaxis, reduce the incidence of dementia?

What does the research evidence say?
Step 1: The Cochrane Library

The Cochrane Library has a relevant systematic review published in 2016 (search conducted November 2015) on the use of statins for the prevention of dementia.[1] This is quite contemporary, but I did a quick check on TripDatabase as well for newer systematic reviews.

Step 2: TripDatabase

I conducted a search using the TripDatabase PICO search tool (Participant: blank, Intervention: "statin", Comparator: "placebo", Outcomes: "dementia"). This identified a pre-appraised critical appraisal on this topic was available from The Mental Elf, which referenced the same Cochrane systematic review. There were other papers on statin withdrawal in dementia (lack of evidence)[2], and statins for the treatment of dementia (insufficient evidence, but probable ineffective).[3]

Let's look at this systematic review by McGuinness and colleagues in detail.[1]

CRITICAL APPRAISAL

I will use the systematic reviews critical appraisal sheet from the Centre for Evidence-Based Medicine.[4]

What PICO question does the systematic review ask?

In people with objectively normal cognitive function and of sufficient age to be at risk of Alzheimer's disease (mean age 65 years or older) (Participants); what is the effect of a statin (used within the licensed dose range) given for at least 12 months (Intervention); compared to placebo (Comparator); on the objective diagnosis of dementia, Alzheimer's disease, and vascular dementia, change in cognition (as measured by MMSE or ADAS-Cog), and incidence and severity of side-effects (Outcome).

Is it clearly stated?

Yes.

Is it unlikely that important studies were missed?

Yes. The search strategy was rigorously

Stat Facts

LEVELS OF EVIDENCE
Evidence from different research methods are ranked as 'levels of evidence'. These levels give an indication of the relative strength and reliability of the evidence for a specific research question. For therapeutic questions, level 1 to level 5 (best to worst) evidence are: (1) systematic reviews of randomised trials, (2) randomised trial, (3) controlled cohort study, (4) case-series, case-control, or historically controlled studies, and (5) mechanism-based reasoning.[8]

described. The primary search was through a specialised register of studies on dementia, which is maintained by the Cochrane Dementia and Cognitive Improvement Group. Multiple additional databases were searched.

Were the criteria used to select articles for inclusion appropriate?
Yes. The authors only included double-blinded randomised trials (RCTs) where the statin was given for at least 12 months. Trials that compared two statins without a placebo arm were excluded.

Were the included studies sufficiently valid for the question asked?
Yes, with caveats. Two large studies were included - the Heart Protection Study (2002)[5], and PROSPER (2002)[6], where the interventions were simvastatin 40mg and pravastatin 40mg respectively. However, only the Heart Protection Study provided data on the incidence of dementia. Although the risk was low in all assessed domains, the incidence rate of dementia was very low.

Were the results similar between studies?
Yes, though not directly. In the analyses on dementia incidence and cognitive change from baseline ("Data and analyses", p. 28[1], only one study or the other provided data to the analyses.

What were the results?
There was no indication from the Heart Protection Study that simvastatin 40mg, as compared to placebo, reduced the incidence of dementia, though the confidence intervals were quite broad:

- Odds ratio: 1.00 (95% CI 0.61 to 1.65), p = 1.0

There was no indication from PROSPER that pravastatin 40mg had any meaningful effect on the MMSE score:

- Mean difference: 0.06 (95% CI -0.04 to 0.16), p = 0.23

DISCUSSION AND CONCLUSION

This systematic review of randomised trials points towards statins having little effect on preventing dementia.

There are some significant limitations. On incidence, only the Heart Protection Study[5] provided data. Although this was a large and very well-performed randomised trial, few participants (fewer than 100 from more than 20,000) were diagnosed with dementia. PROSPER[6] does seem to provide reasonably convincing evidence that pravastatin had no meaningful effect on MMSE score.

Data from observation studies have tended to indicate a protective effect from statins, though biases are probable. A relatively contemporary meta-analysis of eight prospective cohort studies seemed to identify a protective effect, albeit with substantial heterogeneity between the studies.[7] From the perspective of 'levels of evidence' (see Stat Facts), randomised trials provide better evidence than cohort studies, though in this case, judgement needs to be considered when individual randomised trials are compared to a meta-analysis of multiple cohort studies.

My interpretation of the evidence is that the utility of statins as a preventive agent for dementia is not supported by the evidence, but that there remains some ambiguity. Pragmatically, it should not be recommended for this indication alone.

Jonathan and I discussed the evidence and together we made a shared decision not to commence a statin.