Are cholesterol drugs bad for the brain?

I write this article with a bit of trepidation—some may think I'm betraying my "holistic" bona fides.

It's the mainstream medical narrative that cholesterol-lowering drugs are the cornerstone of cardiovascular prevention. I recently listened to a popular podcast that advocated for much more aggressive deployment of these drugs in women, even premenopausally, despite the commonly held belief that women enjoy significant protection from heart disease. The discussants pushed back on the notion that statins don't do much good for women over the age of seventy. They did not address the paradox that women with the highest cholesterols—sometimes over 300—often enjoy the greatest longevity. The podcast minimized the harms of statins, ascribing the majority of reports of muscle aches and weakness to a "nocebo effect". The current trend is toward aggressive lipid therapy—targeting cholesterol reductions of 50% or more in some cases.

On the other hand, stalwarts of natural medicine are often adamantly opposed to cholesterol-lowering. They cite the fact that cholesterol is an important constituent of the lipid bilayers of cell membranes, and that the brain is the body's most cholesterol-laden organ; that cholesterol is the essential precursor of sex hormones and vitamin D; and that a known side effect of statin drugs is their propensity to raise blood sugar and prompt diabetes—surely not a desirable outcome

for cardiovascular prevention.

And, yes, it's true that some patients will complain of brain fog or even full-on Transient Global Amnesia while on statins. Some, diagnosed with dementia, will enjoy a restoration of clarity á la the movie "Awakenings" after statins are deprescribed—I've seen it happen.

So why even prescribe them? Much as I found myself rooting for their failure because of my bias toward lifestyle solutions, after doing a deep dive on the scientific literature, I've taken a more nuanced stance. For secondary prevention, after a heart attack, bypass surgery, or a stent, or in patients with angina, there's clear-cut evidence they reduce risk. But for primary prevention, like the way we use seatbelts to prevent injury in the unlikely event of a car crash, are they warranted in people who merely have "risk factors" like high cholesterol or diabetes?

And the answer is yes, albeit with caveats. It's recently been demonstrated, for people with coronary calcium scores that are negligible or zero, that statins are a waste. And mere high LDL cholesterol is not always a risk factor, if you're lean and metabolically healthy, with vigorous activity levels and following a low-carb anti-inflammatory diet. But for some, statins can and do protect, albeit requiring a high number-needed-to-treat (NNT)—sometimes as high as 50 or 100, meaning 49 to 99 individuals need to be treated to save just one from a bad cardiovascular outcome.

On the other hand, I'm not completely on board with the LDL skeptics, who claim LDL has little to do with cardiovascular risk. It does, but only in the context of other risk factors like high triglycerides, small LDL particle size, Apolipoprotein B, lipoprotein a, highly sensitive C-reactive protein (hsCRP), even homocysteine.

Nor is HDL the get-out-of-jail card we once thought it was: High HDL, while usually protective, isn't always, and low HDL is not always a death knell, especially in Black adults.

What about the brain? I was recently confronted with a therapeutic dilemma while treating a patient with multiple sclerosis. Noting that she had a cholesterol over 300, with an astronomical LDL, I asked her to undergo a heart scan. She came up with a calcium score in the mid-hundreds, indicative of risk. But should I urge her to assent to a statin, which her primary care physician had been pressuring her to take? Would it adversely affect the lipid-rich myelin sheaths which are the targets of her MS autoimmunity?

Consulting the scientific record, I learned there were no studies suggesting statins could worsen MS. In fact, because of their anti-inflammatory effects, there was a hint they could slow MS progression.

Moreover, contrary to the viewpoint of ardent statin foes, most long-term studies don't suggest that decades of statin use lead to dementia. In fact, the opposite trend is sometimes seen: perhaps because certain aspects of brain decline are due to compromised cerebrovascular circulation and inflammation, statins may slow it.

So, I said, try the statin. After all, heart disease remains the main cause of death for women, despite the prevailing belief that it's a "man's disease".

Unfortunately, my patient immediately reported severe muscle pain and leg weakness, typical hallmarks of statin intolerance. Ok, case closed, no statins. Lower doses sometimes ameliorate symptoms, or even substituting red yeast rice, but strong reactors don't usually have luck with those. And Coenzyme Q10 helps only a little if

at all; although vitamin D is sometimes touted as an antidote to statin muscle pain, a recent study demonstrated it doesn't reverse statin myopathy either.

But then her primary care physician proposed a different solution—a PCSK9 inhibitor. These drugs work entirely differently than statins. They're very powerful and can lower LDL to 40 mg/dl or less. They're injectable—usually once a week—and are expensive. Because of their extraordinary price tags, they require insurance approval to qualify and are reserved for people who "fail" statins (i.e. fail to demonstrate sufficient cholesterol-lowering) or don't tolerate them. They're sure to gain traction as new guidelines encourage doctors to play "cholesterol limbo"—how low can you go!

After some deliberation, I agreed she should take the alternative cholesterol med, which surprised my drug-averse patient. After all, I had kept her away from powerful new immunosuppressant drugs for MS—which was the right call because her disease improved with only natural interventions. I had some pangs of conscience because I worried about her brain, and made a mental note to check back with her if I found evidence of harm from this relatively new class of drugs. After all, side effects may take years to emerge, and even if the safety of dramatically slashing cholesterol were to be demonstrated in early approval trials, they might prove harmful in the long run.

We have reason to question even randomized controlled trials of medications. For example, PCSK9 inhibitor drugs may show benefits and no harm in studies, but it may be that more affluent, more compliant, and health-conscious persons who have better access to pricey medical care take them, and hence seem to do better than their less proactive peers. But a new type of study appears to sidestep these confounders: Mendelian randomization.

While rare, there's a gene variation that endows a small number of individuals with a PCSK9 advantage. They have very low cholesterol regardless of diet or lifestyle, and they enjoy considerable protection against heart disease. They may be poor, rich, fat, thin, indiscriminate or scrupulous about diet, sedentary or active, get regular checkups or not—but the one thing they have in common is hard-wired PCSK9 inhibition. And they have it for a lifetime, which should reveal long-term harmful effects of cholesterol deprivation on the brain, if such exists.

According to a recent Mendelian randomization study of PCSK9 inhibition, there were *no* adverse brain effects. I felt reassured about my patient, and I worry less about the long-term effects on my patients of these powerful drugs—whose popularity is only likely to increase.

On the other hand, the same study found small but real "adverse neurocognitive effects" with statins, which prompted the authors to hedge:

" . . . we emphasize that any potential adverse effects of HMGCR inhibition on neurocognition found in this study likely do not outweigh the cardiovascular benefits of statin use."

As for statins, there may be a solution: Certain statin drugs are lipophilic (Lipitor, Zocor), which means they readily cross the blood-brain barrier; others are non-lipophilic (Crestor, Pravachol), confining their protective effects to blood vessels outside the brain. I'll preferentially prescribe the latter, except in stroke survivors, where protection of brain arteries may be advisable.

But I'll stay conservative about condoning cholesterol drugs for my patients because I continue to believe in the primacy of lifestyle for cardiovascular prevention. I

now also acknowledge that sometimes that’s not enough—good medicine is not an either/or.