

Could Statins Do More Than Lower Cholesterol in Patients With COVID-19?

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Practically every day this spring, New York University cardiologist Aakriti Gupta, MD, MS, has received a phone call from friends or relatives in India who have COVID-19. They want to know whether they should start taking statins, which are cheap and available without a prescription in Gupta's COVID-19-ravaged homeland.

A history of myocardial infarction, congestive heart failure, and hyperlipidemia have all been associated with an increased risk of in-hospital mortality from COVID-19. Observational studies by Gupta and others have suggested that taking statins might not only lower blood cholesterol levels, but also reduce the risk of dying from COVID-19.

Statins do more than lower cholesterol, Gupta noted in an interview. They have both anti-inflammatory and antithrombotic properties, which could make them an attractive class of drugs for treating COVID-19, Gupta and her coauthors suggested in a May 2020 [article](#).

Preclinical studies indicate that statins could worsen COVID-19 or at least increase the chances of infection, Italian researchers pointed out in a recent *JAMA Internal Medicine* [article](#). That's because statins, along with several other classes of drugs used to treat atherosclerotic heart disease and its risk factors, upregulate angiotensin-converting enzyme 2 (ACE2) receptors, which happen to be SARS-CoV-2's gateway into cells. Yet theoretically, the authors noted, the same drugs may improve the clinical course of COVID-19 by reducing vasoconstriction, inflammation, and oxidation.

Mixed Findings

So far, most studies examining whether statins might benefit people with COVID-19 have been retrospective analyses of hospitalized patients. To try to mimic randomized clinical trials, researchers have matched patients who'd been taking statins with those who had not on the basis of such factors as vital signs, laboratory values, and body mass index—a method called propensity-score matching.

Their findings haven't consistently linked the drugs with a lower short-term risk



of dying after contracting COVID-19. These observational studies found an association between statin use and lower mortality among patients with COVID-19:

- In an article published earlier this year, Gupta and her colleagues found that among 1296 New York City patients hospitalized with COVID-19, 26.5% of patients who hadn't been taking statins died within 30 days of hospital admission compared with 14.8% of patients who used the drugs.
- Wayne State University researchers found that in a cohort of 466 patients hospitalized with COVID-19, those who had been taking moderate or high doses of statins, but not low doses, had a significantly reduced risk of dying compared with those who had not been taking statins. The study didn't find a significant association between statin use and intensive care unit (ICU) admission or the need for mechanical ventilation.
- A study of 1179 patients with COVID-19 in Massachusetts General Hospital that has not yet been peer-reviewed found that statin use during hospitalization, newly initiated or not, was associated with improved 28-day mortality for patients older than 65 years but not for patients 65 years or younger.
- In a study of nearly 14 000 patients hospitalized with COVID-19 in Hubei Province, China, 5.2% of statin users compared with 9.4% of matched statin nonusers died of any cause.

On the other hand, some studies have found no association between statin use and lower COVID-19 death rates:

- A meta-analysis of 9 studies conducted in the US, China, and elsewhere concluded that statin use wasn't associated with reduced severity or death among patients hospitalized with COVID-19.
- Using data from Danish nationwide registries, researchers found no difference in all-cause mortality between statin users and nonusers among people with COVID-19, regardless of whether they were hospitalized.
- The aforementioned Italian study in *JAMA Internal Medicine* analyzed data from about 4000 patients with confirmed COVID-19 in Lombardy, Italy, ICUs. Long-term treatment with statins, ACE inhibitors, diuretics, β -blockers, angiotensin II receptor blockers, antiplatelet drugs, and anticoagulants before admission was associated with higher mortality but only in an unadjusted analysis. Unmeasured confounders, as opposed to the drugs themselves, could explain that observation, the authors noted.

Don't Start, Don't Stop

Given a lack of randomized clinical trial data to support such a recommendation, no one is yet advising that people for whom statins aren't indicated start taking the drugs to lower their risk of dying from COVID-19.

Guidelines from the [National Institutes of Health](#) go only as far as advising that patients with COVID-19 who were already taking statins continue to do so. [Massachusetts General Hospital](#) advises that if patients with COVID-19 aren't already taking statins, only those who have an indication for the drugs and no contraindications should start taking them.

Unanswered Questions

Because observational studies have focused on hospitalized patients, the generalizability of their results to people with COVID-19 who aren't hospitalized is limited, the Wayne State researchers pointed out. They also noted that patients who take statins might generally be more health-conscious than nonusers and, therefore, manage their comorbidities better and seek care earlier in the course of COVID-19.

As Gupta and others have emphasized, only randomized controlled trials could show whether statin use itself or other characteristics of statin users might contribute to a lower risk of death from COVID-19.

Preliminary results from one such study, for which Gupta serves on the steering com-

mittee, were presented May 16 at a [late-breaking clinical research session](#) at the American College of Cardiology (ACC) meeting.

The [trial](#) involved ICU patients with COVID-19 in Iran. It was designed to answer 2 primary questions: whether a higher anticoagulant dose or a newly prescribed statin could reduce the risk of dying within 30 days of hospital admission. Patients were randomized to a higher dose or standard dose of anticoagulant therapy, and then each of those groups was randomized to 20 mg per day of atorvastatin or a placebo.

The higher anticoagulant dose did not reduce mortality, the authors [reported](#) recently in *JAMA*. Because the statin vs placebo arm of the trial excluded people who'd already been taking statins, more patients had to be enrolled to reach a goal of 600 needed to adequately power that arm, and it was unblinded only in early May, principal investigator Behnood Bikdeli, MD, MS, said in an interview.

At the ACC meeting, Bikdeli reported [findings](#) from the study's statin group that were similar to the anticoagulant group findings. Twenty milligrams per day of atorvastatin did not reduce 30-day mortality compared with the placebo, said Bikdeli, a physician-investigator in cardiovascular medicine at the Brigham and Women's Hospital who is originally from Iran.

Still, Bikdeli said, he holds out hope for statins' usefulness in treating some pa-

tients with COVID-19. A subgroup analysis of his data found fewer deaths and blood clots in 1 group: those who were admitted to the ICU within 7 days of their first symptoms. "This is not sufficient to change practice," he said, "but I think it's very important to pursue in future studies."

In addition, Bikdeli said, the trial results don't rule out the possibility that initiating statin therapy might help patients with COVID-19 who don't require ICU care, including people with [long COVID](#) who have persistent symptoms. Or, perhaps, doubling the atorvastatin dose would be effective in the ICU, Bikdeli said, adding that he is considering a trial to answer that question.

"It's not early in the pandemic anymore," he said. "We need data to guide management."

The Upshot

For now, when friends and family with COVID-19 ask whether they should start taking statins, Gupta said, "I would suggest it only if there was an indication." In other words, she wouldn't advise otherwise healthy 30-year-olds with COVID-19 to take statins, but many of her callers from India are older and overweight and, likely, have unfavorable blood lipid profiles.

"Just take statins," she tells them. "You probably should already be on them." ■

Note: Source references are available through embedded hyperlinks in the article text online.