Study finds residual inflammation after statin therapy strongly predicts cardiovascular events, death

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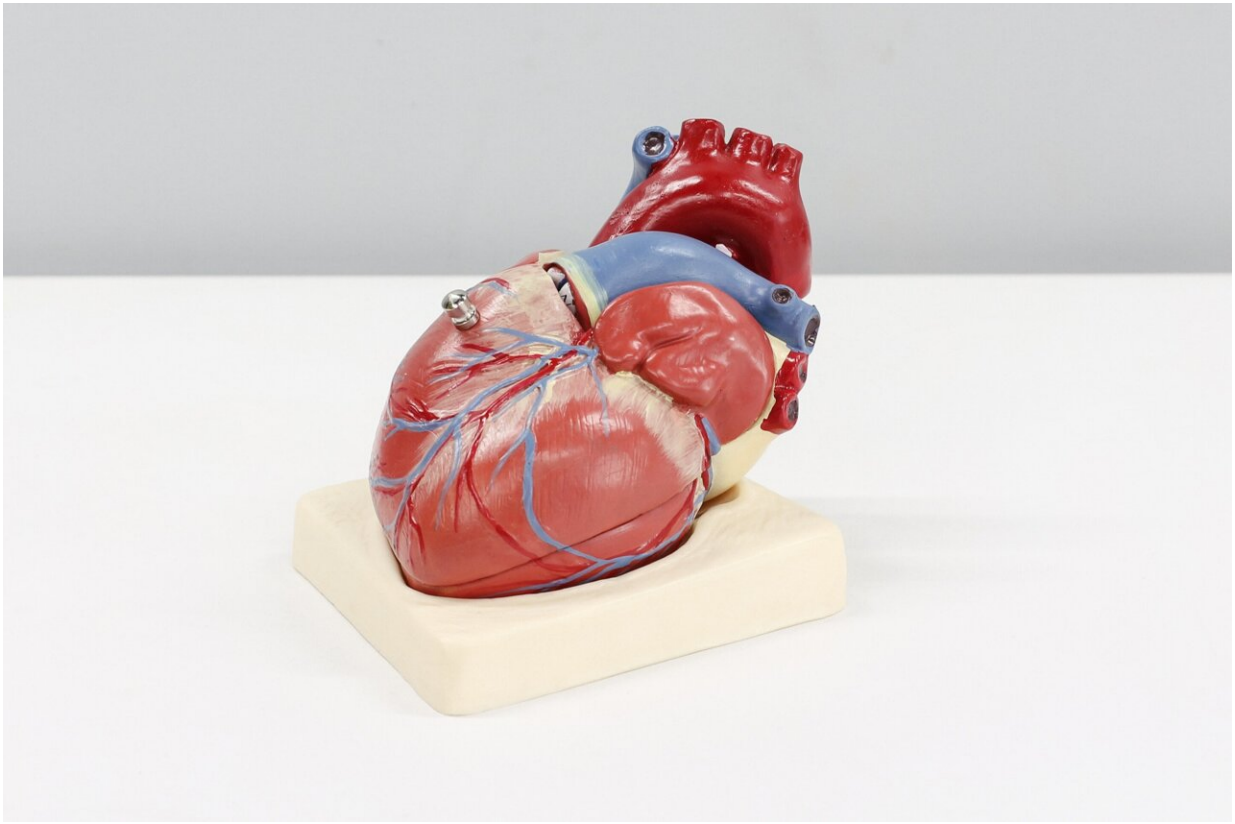

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New evidence released today from a study of 31,245 patients already taking statin therapy indicates that inflammation may be a more

powerful predictor of risk of future cardiovascular events—such as heart attack and stroke—than "bad" cholesterol.

Treatments that aggressively lower vascular inflammation need to be incorporated into daily practice if doctors are to maximize patient outcomes, according to the study's corresponding author, Paul Ridker, MD, a preventive cardiologist at Brigham and Women's Hospital, a founding member of the Mass General Brigham health care system. Ridker presented the findings at the American College of Cardiology meeting in New Orleans. Results are published simultaneously in *The Lancet*.

"The new data should be a wake-up call for preventive cardiologists and their patients," said Ridker. "Virtually all patients with or at risk for atherosclerotic disease are appropriately treated with aggressive statin therapy. Yet, in our study of patients already taking a statin, hsCRP—a measure of residual inflammatory risk—was a more powerful determinant of having a future heart attack or dying from cardiovascular disease than was LDL-cholesterol—a measure of residual cholesterol risk. The data are a powerful demonstration that to beat heart disease, we need to lower both cholesterol and inflammation, not just cholesterol alone."

Once a patient is on statin therapy, cardiologists typically describe two conditions: "residual cholesterol risk," which can be further reduced with additional lipid-lowering therapy, and "residual inflammatory risk," which can be further reduced with certain drugs that impact vascular inflammation. Whether clinicians should choose to focus on further lowering cholesterol or inflammation has been uncertain and controversial.

Ridker and colleagues examined data from three recently conducted clinical trials (PROMINENT, REDUCE-IT and STRENGTH) of

patients with or at high risk for atherosclerotic disease to understand the relative importance of "residual inflammatory risk" as compared to "residual cholesterol risk" among contemporary statin-treated patients.

All patients were receiving aggressive guideline directed medical care including statins, usually at high doses. But cardiovascular event rates in all three trials approached 10 percent at five years. In all three trials, blood levels of high-sensitivity C-reactive protein (hs-CRP, a measure of vascular inflammation) were significantly associated with major adverse cardiovascular events (MACE), cardiovascular mortality and all-cause mortality.

Moreover, the researchers report that hs-CRP was a more potent predictor of future cardiovascular risk than LDL-cholesterol. For example, among aggressively treated patients already on higher intensity statins, the risks of cardiovascular death and all-cause mortality were more than twice as high among those with the highest levels of CRP when compared to those with the highest levels of cholesterol, differences that were highly statistically significant.

The data have immediate implications for patient care today and for future research, according to the authors.

"There is no doubt that lower is better for LDL-cholesterol and we need to aggressively reduce cholesterol whenever possible. But if cardiologists want to eliminate cardiovascular disease, they clearly must target inflammation as well," Ridker said.

Inflammation inhibition has been found in several clinical trials to reduce cardiovascular risk, yet uptake of anti-inflammatory therapy in daily practice has been limited. This has been particularly true for colchicine, an inexpensive anti-inflammatory therapy that reduced cardiovascular event rates in two major randomized trials with a benefit

at least as large as that associated with much more expensive cholesterol -lowering drugs. Ridker notes the importance of weighing the potential benefits of anti-inflammatory agents, in addition to statin therapy and lifestyle modifications, to lower cardiovascular risk.

"Beyond statins and consideration of anti-inflammatory agents, physicians should not lose sight of diet, exercise, and smoking cessation, all of which lower vascular inflammation and save lives," Ridker said.

More information: Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials, *The Lancet* (2023). DOI: 10.1016/S0140-6736(23)00215-5

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