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OP-ED CONTRIBUTOR

What's Cholesterol Got to Do With It?

By GARY TAUBES

THE idea that cholesterol plays a key role in heart disease is so tightly woven into modern medical thinking that it is no longer considered open to question. This is the message that emerged all too clearly from the recent news that the drug Vytorin had fared no better in clinical trials than the statin therapy it was meant to supplant.

Vytorin is a combination of cholesterol-lowering drugs, one called Zetia and the other a statin called Zocor. Because the two drugs lower LDL cholesterol by different mechanisms, the makers of Vytorin (Merck and Schering-Plough) assumed that their double-barreled therapy would lower it more than either drug alone, which it did, and so do a better job of slowing the accumulation of fatty plaques in the arteries — which it did not.

Heart disease specialists who were asked to comment on this turn of events insisted that the result implied nothing about their assumption that LDL cholesterol is dangerous, only about whether it is always medically effective to lower it.

But this interpretation is based on a longstanding conceptual error embedded in the very language we use to discuss heart disease. It confuses the cholesterol carried in the bloodstream with the particles, known as lipoproteins, that shuttle that cholesterol around. There is little doubt that certain of these lipoproteins pose dangers, but whether cholesterol itself is a critical factor is a question that the Vytorin trial has most definitely raised. It's a question that needs to be acknowledged and addressed if we're going to make any more headway in preventing heart disease.

To understand the distinction between cholesterol and lipoproteins it helps to know something of the history of cholesterol research.

In the 1950s, two hypotheses competed for attention among heart disease researchers. It had been known for decades that cholesterol was a component of atherosclerotic plaques, and people who have a genetic disorder that causes extremely high cholesterol levels typically have clogged arteries and heart attacks. As new technology enabled them to look more closely at lipoproteins, however, researchers began to suspect that these carrier molecules might play a greater role in

cardiovascular disease than the cholesterol inside them. The cholesterol hypothesis dominated, however, because analyzing lipoproteins was still expensive and difficult, while cholesterol tests were easily ordered up by any doctor.

In the late 1960s, biochemists created a simple technique for measuring, more specifically, the cholesterol inside the different kinds of lipoproteins — high-density, low-density and very low-density. The National Institutes of Health financed a handful of studies to determine whether these "cholesterol fractions" could predict the risk of cardiovascular disease. In 1977, the researchers reported their results: total cholesterol turned out to be surprisingly useless as a predictor. Researchers involved with the Framingham Heart Study found that in men and women 50 and older, "total cholesterol per se is not a risk factor for coronary heart disease at all."

The cholesterol in low-density lipoproteins was deemed a "marginal risk factor" for heart disease. Cholesterol in high-density lipoproteins was easily the best determinant of risk, but with the correlation reversed: the higher the amount, the lower the risk of heart disease.

These findings led directly to the notion that low-density lipoproteins carry "bad" cholesterol and high-density lipoproteins carry "good" cholesterol. And then the precise terminology was jettisoned in favor of the common shorthand. The lipoproteins LDL and HDL became "good cholesterol" and "bad cholesterol," and the lipoprotein transport vehicle was now conflated with its cholesterol cargo. Lost in translation was the evidence that the causal agent in heart disease might be abnormalities in the lipoproteins themselves.

The truth is, we've always had reason to question the idea that cholesterol is an agent of disease. Indeed, what the Framingham researchers meant in 1977 when they described LDL cholesterol as a "marginal risk factor" is that a large proportion of people who suffer heart attacks have relatively low LDL cholesterol.

So how did we come to believe strongly that LDL cholesterol is so bad for us? It was partly due to the observation that eating saturated fat raises LDL cholesterol, and we've assumed that saturated fat is bad for us. This logic is circular, though: saturated fat is bad because it raises LDL cholesterol, and LDL cholesterol is bad because it is the thing that saturated fat raises. In clinical trials, researchers have been unable to generate compelling evidence that saturated fat in the diet causes heart disease.

The other important piece of evidence for the cholesterol hypothesis is that statin drugs like Zocor and Lipitor lower LDL cholesterol and also prevent heart attacks. The higher the potency of statins, the greater the cholesterol lowering and the fewer the heart attacks. This is perceived as implying cause and effect: statins reduce LDL cholesterol and prevent heart disease, so reducing LDL cholesterol prevents heart disease. This belief is held with such conviction that the Food and

Drug Administration now approves drugs to prevent heart disease, as it did with Zetia, solely on the evidence that they lower LDL cholesterol.

But the logic is specious because most drugs have multiple actions. It's like insisting that aspirin prevents heart disease by getting rid of headaches.

One obvious way to test the LDL cholesterol hypothesis is to find therapies that lower it by different means and see if they, too, prevent heart attacks. This is essentially what the Vytorin trial did and why its results argue against the hypothesis.

Other such tests have likewise failed to confirm it. A recent trial of torcetrapib, a drug that both raises HDL and lowers LDL cholesterol, was halted midstream because the drug seemed to cause heart attacks and strokes rather than prevent them. Estrogen replacement therapy also lowers LDL cholesterol, but it too has failed to prevent heart disease in clinical trials. The same goes for eating less saturated fat.

So it is reasonable, after the Vytorin trial, to question the role of LDL cholesterol in heart disease. Not whether statins help prevent heart disease, but whether they work exclusively, or at all, by this mechanism.

There are numerous other ways in which statins might be effective. They reduce inflammation, which is now considered a risk factor for heart disease. They act to keep artery walls healthy. And statins act on lipoproteins as much as on the cholesterol inside them. They decrease the total number of low-density and very low-density lipoproteins in the blood, including the smallest and densest form of LDL, which is now widely believed to be particularly noxious.

Because medical authorities have always approached the cholesterol hypothesis as a public health issue, rather than as a scientific one, we're repeatedly reminded that it shouldn't be questioned. Heart attacks kill hundreds of thousands of Americans every year, statin therapy can save lives, and skepticism might be perceived as a reason to delay action. So let's just trust our assumptions, get people to change their diets and put high-risk people on statins and other cholesterol-lowering drugs.

Science, however, suggests a different approach: test the hypothesis rigorously and see if it survives. If the evidence continues to challenge the role of cholesterol, then rethink it, without preconceptions, and consider what these other pathways in cardiovascular disease are implying about cause and prevention. A different hypothesis may turn out to fit the facts better, and one day help prevent considerably more deaths.

Gary Taubes is the author of "Good Calories, Bad Calories: Challenging the Conventional Wisdom on Diet, Weight Control and Disease."