74.6 decibels—not loud enough to damage hearing, he says.

Reports that some diplomats suffered brain trauma also undermine the acoustic attack hypothesis. In medical procedures, ultrasound is used to destroy brain tumors, but it attenuates rapidly with distance. The Cubans also concluded that the reported symptoms imply more serious brain injuries than anyone is alleging—and some U.S. researchers agree. "The combination of sudden onset of hearing loss, tinnitus, headaches, vertigo, nausea, insomnia, anxiety, and memory problems would have to be related to multiple lesions in both brain hemispheres," says neurologist Alberto Espay of the University of Cincinnati in Ohio, who has read the Cuban report. Based on what little the State Department has revealed, he says, that "wasn't the case here."

The Cuban panel evaluated other possible causes of the symptoms. For instance, U.S. officials questioned whether aerial fumigation to kill mosquitoes could be the culprit. The insecticide of choice in Cuba is permethrin, which in acute doses can cause nausea, headaches, and shortness of breath. The Cuban team found no evidence of excessive use of the fumigant, Kuscevic says.

"We have devoted months to this work, but we have not found any evidence that could substantiate [the U.S.] claims," says panel member Antonio Paz Cordovéz, president of the Cuban Society of Otorhinolaryngology here. He and his colleagues kept circling back to the idea of mass stress. Around the time the first diplomats here fell ill, the U.S. embassy was bracing for a downturn in relations. President Donald Trump had just won the election, and he had vowed to slow or reverse the rapprochement that his predecessor had begun.

"That kind of situation leads you to feel threatened," says panelist Dionisio Zaldívar Pérez, a psychologist at Havana University. He believes the U.S. government fueled anxiety by labeling the illnesses an attack. In the "very closed community of English-speaking diplomats who have few connections with the Cuban population," Valdés-Sosa adds, stress could quickly escalate. "U.S. neurologists provided with the evidence given to the Cuban committee would have arrived at the same conclusion," Espay says.

Valdés-Sosa, a neurophysiologist, emphasizes that the panel's findings are provisional. "If any evidence were available, we would be willing to revise our conclusions," he says. And they are eager to team up with U.S. scientists. That's unlikely, in the present climate. But Rasenick says joint research "would bring benefit to both diplomacy and to those diplomats reporting health problems." ■

BIOMEDICINE

To help save the heart, is it time to retire cholesterol tests?

Measuring a blood protein, apoB, might save more lives

By **Mitch Leslie**

The next time you go in for a medical checkup, your doctor will probably make a mistake that could endanger your life, contends cardiologist Allan Sniderman of McGill University in Montreal, Canada. Most physicians order what he considers the wrong test to gauge heart disease risk: a standard cholesterol readout, which may indicate levels of low-density lipoprotein (LDL) or non–high density lipoprotein (non-HDL) cholesterol. What they should request instead, Sniderman argues, is an inexpensive assay for a blood protein known as apolipoprotein B (apoB).

ApoB indicates the number of cholesterol-laden particles circulating in the blood—a truer indicator of the threat to our arteries than absolute cholesterol levels, some researchers believe. Sniderman asserts that routine apoB tests, which he says cost as little as $20, would identify millions more patients who could benefit from cholesterol-cutting therapies and would spare many others from unnecessary treatment. "If I can diagnose [heart disease] more accurately using apoB, and if I can treat more effectively using apoB, it's worth 20 bucks," he says.

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>
> **Robert Eckel**, University of Colorado School of Medicine

Sniderman and a cadre of other scientists have been stumping for apoB for years, but recent reanalyses of clinical data, together with genetic studies, have boosted their confidence. At last month's American Heart Association (AHA) meeting in Anaheim, California, for example, Sniderman presented a new take on the National Health and Nutrition Examination Survey (NHANES), a famous census of the U.S. population's health. The reexamination, which compared people with different apoB levels but the same non-HDL cholesterol readings, crystallizes the importance of measuring the protein, he says. Across the United States, patients who have the highest apoB readings will suffer nearly 3 million more heart attacks, strokes, and other cardiovascular events in the next 15 years than will people with the lowest levels, Sniderman reported. As lipidologist Daniel Rader of the University of Pennsylvania Perelman School of Medicine puts it, the question of whether LDL cholesterol is the best measure of cardiovascular risk now has a clear answer: "No."

But plenty of scientists disagree. "Many lines of evidence say there's not a lot more predictive power of apoB over LDL cholesterol," says cholesterol researcher Scott Grundy of the University of Texas Southwestern Medical Center in Dallas, who has helped craft several sets of cardiology care guidelines. And changing clinical practice would be disruptive. Standard heart disease risk guidelines downplay or omit apoB, and the algorithms that help doctors decide which patients to treat don't incorporate it.

ApoB backers have a new opportunity to make their case. A committee of researchers and doctors is reworking the most influential U.S. recommendations for cholesterol treatment, published by the American College of Cardiology (ACC) and AHA, and should issue an update next year. The European equivalents are also being revamped, although a new version won't be ready for 2 to 3 years, says cardiologist and genetic epidemiologist Brian Ference of the University of Cambridge in the United Kingdom, who is taking part in the rewrite.

Nobody expects these latest revisions to jilt cholesterol for apoB, but its advocates say there's increasing science on their side. Cholesterol cruises through our blood in

several kinds of protein-containing particles, including HDLs, LDLs, and very low-density lipoproteins (VLDLs). When certain particles, such as LDLs and VLDLs, depart the bloodstream and get stuck in the lining of our arteries, atherosclerosis can result. Total cholesterol level was the first widely used indicator of this risk, but after researchers discovered that one form of cholesterol, HDL, may be protective, LDL cholesterol became the benchmark. Now, some physicians favor non-HDL cholesterol, which encompasses multiple cholesterol types, including LDL and VLDL.

All of these measures, however, reveal the amount of lipid in the blood, rather than the number of cholesterol-hauling particles. ApoB, in contrast, provides a direct measure of their abundance because each LDL or VLDL particle contains a single copy of the protein.

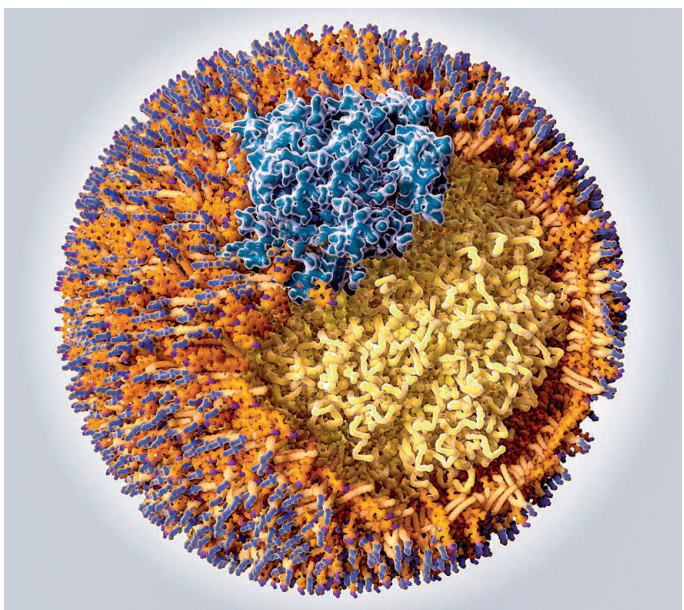
Still, even apoB advocates admit that LDL cholesterol's track record is pretty good. About 85% of the time, it provides an accurate indication of a patient's likelihood of developing cardiovascular disease, Ference says. But that means it's wrong 15% of the time, he adds.

A 2009 study found that nearly half of patients admitted to hospitals because of heart attacks had normal or low LDL levels. So by measuring LDL alone, doctors risk overlooking people who need treatment or, if they are already taking drugs to trim their cholesterol levels, a more intensive regimen.

At the same time, some people taking drugs for what seem to be dangerously high LDL cholesterol levels may not need treatment, Sniderman says. A more discriminating test for cardiovascular risk could spare these people from potential side effects and save money. Although cholesterol-lowering statins are cheap, Sniderman notes that newer drugs given when statins aren't enough, such as the PCSK9 inhibitors, can cost tens of thousands of dollars per year.

Switching to measuring apoB would improve diagnoses because it better reflects the mechanism of cardiovascular disease, according to Sniderman. "The data support that it's the LDL particles themselves that are the bad actors," rather than the cholesterol they contain, Rader says. The more of these particles that course through a patient's blood, the more get stuck in the arterial walls and the higher the probability of cardiovascular disease. Because LDL cholesterol and apoB are intertwined, both measures give the same result for many patients. However, the amount of cholesterol a particle contains can vary. So LDL cholesterol levels can be misleading for patients who have few large particles or many small ones.

No current drugs drive down just apoB, making its impact difficult to untangle from the effect of lowering cholesterol overall. But in a 2015 paper, Sniderman and colleagues reanalyzed data from the famous Framingham Heart Study, which has been probing the causes of cardiovascular disease for nearly 70 years. The patients with the best odds of surviving for at least 20 years had low levels of apoB and non-HDL cholesterol, the team found. But the patients with the worst chances had high levels of apoB, even though their non-HDL cholesterol was low. Similarly, the reassessment of the NHANES data that Sniderman presented at the AHA meeting suggests that apoB is a better predictor of risk.



In this illustration of a low-density lipoprotein particle, apolipoprotein B (blue) is surrounded by various forms of cholesterol (orange and yellow) and other lipids.

Also pointing to apoB's importance is a type of analysis in which researchers comb through genetic data from large numbers of patients to identify gene variants that influence a particular trait. Scientists then track the variants' sway on health, a method called Mendelian randomization because it relies on accidents of heredity to create comparison groups. "It's essentially nature's randomized trial," Ference says. In a study in *The Journal of the American Medical Association* in September, he and his colleagues dissected the impact of variants of two genes involved in cholesterol metabolism: *CETP* and *HMGCR*.

Using data from more than 100,000 patients, the researchers found that people with sluggish versions of the enzyme encoded by *CETP* showed equivalent reductions in apoB and LDL cholesterol levels and were less likely than people with vigorous versions of the enzyme to suffer cardiovascular crises such as heart attacks or strokes. But the scientists saw a telling difference when they analyzed patients who also produced underactive versions of *HMGCR*'s enzyme. Although these people showed further decreases in LDL cholesterol, their apoB levels—and their cardiovascular risk—didn't decline by as much. That discrepancy suggests that reducing apoB has a bigger protective effect than lowering LDL, Ference says.

The picture is clear, says preventive cardiologist Seth Martin of Johns Hopkins University School of Medicine in Baltimore, Maryland. "The totality of evidence is in favor of apoB being an important marker that can identify risk even when LDL is controlled."

But would the gains be worth the disruption? "The poor frontline primary care doctor doesn't want to have to think about apoB and non-HDL cholesterol," says preventive cardiologist and epidemiologist Jennifer Robinson of the University of Iowa in Iowa City, who was vice chair of the committee that drafted the most recent ACC/AHA recommendations in 2013. "It's too much information—and when you give people too much information they ignore it."

Cardiologist Robert Eckel of the University of Colorado School of Medicine in Aurora, who was also on the ACC/AHA committee, agrees. "I don't see apoB changing the playing field very much," he says.

Many apoB advocates reluctantly concur. LDL cholesterol is deeply entrenched in medical routines, and "it's not going to change any time soon," Rader says. "I go from depression to worse depression," Sniderman says.

But if future guidelines start to emphasize apoB's diagnostic value and drug companies begin to target it, Ference thinks physicians will eventually pay heed to the protein. "The argument is that LDL cholesterol is good enough," he says. "But as we move toward more personalized medicine, it's not." ■

ILLUSTRATION: JUAN GAERTNER/SCIENCE SOURCE

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