Is apolipoprotein B the best measure of CVD risk?

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November 2022—The evidence in favor of measuring apolipoprotein B routinely, with other lipid parameters, is now so overwhelming, says cardiologist Allan Sniderman, MD, that he believes it's unreasonable to deny patients the advantage of apoB.

"If evidence is what counts," he says, "then the care Americans receive should include apoB." ApoB measurement would "simplify, unify, and clarify," and without it patients and physicians have only a partial picture, he says.

Dr. Sniderman, Edwards professor of cardiology and professor of medicine, McGill University, speaking at the AACC annual meeting and recently with CAP TODAY, said, "When your LDL or non-HDL cholesterol are measured, you may not have an accurate idea of the risk posed to you." The true cardiovascular disease risk may be higher or lower, "and in this day and age," he said, "that should be unacceptable."

In fact, measurement of apoB, which is the sum of all atherogenic particles, should be the primary marker, he said. "It's not the whole story. Lp(a) matters, triglycerides matter for pancreatitis and type three hyperlipoproteinemia. Moreover, apoB is certainly not the end of the road in characterization," he said. But without an apoB measurement, "you haven't even begun to take the first step on the road," and it's one that "will take you a long way down the road."

ApoB is better than other cholesterol markers because the number of apoB particles in the lumen is the primary determinant of the number that get into the arterial wall and become trapped, said Dr. Sniderman, who is also director of the Mike Rosenbloom laboratory for cardiovascular research, Royal Victoria Hospital, Montreal. And trapping of the apoB particles within the wall is the fundamental cause of atherosclerosis. Cholesterol within the trapped particles is strongly proatherogenic, and the relationships demonstrated between risk and the levels of LDL-C and non-HDL-C are true. So too is the correlation between lowering levels of LDL-C and non-HDL-C and better outcomes. "But it's also equally true that cholesterol within the wall only got there within an apoB particle. It got transported in and trapped."

Dr. Sniderman

Cholesterol is "not the only poison in the particle," Dr. Sniderman said. "The apoB, when it's oxidized and breaks and is degraded, is strongly proatherogenic," as are the phospholipids when they're oxidized. "It's the particle that matters."

Smaller, cholesterol-poor apoB particles are trapped more avidly within the arterial wall than larger apoB particles and bind more easily to the glycosaminoglycans, he said. Larger, cholesterol-rich apoB particles deposit more cholesterol when trapped within the arterial wall. "VLDL particles are atherogenic—they tend to have more cholesterol in them." But when looked at in totality, "they tend to be equally atherogenic within the limits of detection."

"Maybe there are some differences," Dr. Sniderman said. "But the tools we have to measure differential atherogenicity don't allow us to separate anything out. So at the moment, apoB is the accurate sum of all the atherogenic particles, and that's the most important measure you can make."

The 2019 European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidemias to reduce cardiovascular risk concluded that apoB is a more accurate marker of risk and adequacy of therapy than LDL-C or non-HDL-C, Dr. Sniderman said. And they said that apoB can be measured inexpensively—using widely available, automated, standardized methods—and more accurately, particularly at low concentrations, than LDL-C or non-HDL-C. That apoB can be measured inexpensively and accurately is also in AACC's 2009 and 2013 lipoprotein guidelines, he noted. "But is it being measured in the U.S.? No. What is one of the primary arguments against it? That it can't be measured more accurately. And that's nonsense."

The United States lipid community "led the world" on cholesterol, he said, with major achievements: linking cholesterol—in particular LDL-C—to the risk of atherosclerotic cardiovascular disease, developing algorithms to estimate the short-term risk of atherosclerotic CVD, demonstrating that the LDL receptor pathway is a genetic cause of familial hypercholesterolemia and a major determinant of the levels of LDL-C in plasma, developing statin therapies (Al Alberts of Merck), and creating scientific training opportunities for non-American scientists, among them Dr. Sniderman. "You did it. This is the most positive, wonderful country when you're on your game," he said.

However, neither the U.S. nor Canadian lipid communities have led the world in realizing the limitations of the LDL-receptor pathway as a determinant of the concentrations of LDL-C and apoB in plasma, he said (Sniderman AD, et al. *J Am Coll Cardiol.* 2022;79[10]:1023–1031). They have not accepted the now "overwhelming evidence" that apoB is a more accurate marker of atherosclerotic CVD risk and a more accurate index of the adequacy of lipid-lowering therapy than LDL-C or non-HDL-C, and that it can be measured more accurately, particularly at low concentrations.

As evidence, Dr. Sniderman cites many prospective observational studies that found apoB to be superior to LDL-C in assessing CVD risk, including the Québec Cardiovascular Study, Northwick Park Heart Study, Framingham Heart Study, Copenhagen City Heart Study, the Interheart and Interstroke studies, and others. Two prospective studies (Emerging Risk Factors Collaboration and Atherosclerosis Risk in Communities) found apoB equal to LDL-C in risk assessment. "But primarily they were based on whether it changed the c-statistic, and that's irrelevant," he said. They found "total cholesterol was just as good as anything, which is nonsense."

Five Mendelian randomization studies found apoB superior to LDL-C in predicting coronary heart disease (Richardson TG, et al. *PLoS Med.* 2020;17[3]:e1003062; Zuber V, et al. *Int J Epidemiol.* 2021;50[3]:893–901; Yuan S, et al. *Ann Neurol.* 2020;88[6]:1229–1236; Levin MG, et al. *Circulation.* 2021;144[5]:353–364; Richardson TG, et al. *Lancet Healthy Longev.* 2021;2[6]:e317–e326). Seven prospective observational studies found apoB to be equal to non-HDL-C as a marker, and nine prospective observational epidemiological studies found it to be superior to non-HDL-C. "There are more that show apoB wins," he noted. (For example: Steffen BT, et al. *Arterioscler Thromb Vasc Biol.* 2015;35[2]:448–454; Marston NA, et al. *JAMA Cardiol.* 2022;7[3]:250–256; O'Donnell MJ, et al. *J Stroke.* 2022;24[2]:224–235.)

In a 2019 paper, Dr. Sniderman and coauthors illustrated discordance in LDL-C and apoB when the apoB particles contain an average mass of cholesterol, when they are cholesterol-enriched, and when they are cholesterol-depleted (Sniderman AD, et al. *JAMA Cardiol.* 2019;4[12]:1287–1295). "Simply because the absolute hazard ratio for LDL-C/non-HDL-C are equal in a study does not mean they predict risk equally in an individual with cholesterol-loaded or cholesterol-depleted apoB particles," he said.

To show what that means to an individual, Dr. Sniderman created the profile of a patient with cholesterol-depleted apoB particles who had an LDL-C of 111 mg/dL, non-HDL-C of 134 mg/dL, and apoB of 115 mg/dL. He assigned the patient a hazard ratio of 1.20 and two standard deviations. "This is small dense LDL," he said.

"In any individual, when apoB particles are either cholesterol-loaded or -depleted, the risk predicted by LDL-C/non-HDL-C and apoB will not be equal," he said. The predicted increase in the individual's CVD risk was 44 percent based on the patient's LDL-C and non-HDL-C, whereas the apoB-predicted increased risk was 73 percent, Dr. Sniderman said.

In patients who are discordant based on the amount of cholesterol in their apoB particles, the apoB and cholesterol

markers will predict differently, even if the hazard ratio is the same, he said. “That’s the core idea in discordance analysis.” Conventional statistical methods were not designed to deal with highly correlated variables like LDL-C, non-HDL-C, and apoB. “And that’s been used as an argument for saying they’re equivalent,” Dr. Sniderman said. Discordance analysis was designed to directly contrast risk predictions by highly correlated variables.

Dr. Sniderman and coauthors studied a Framingham offspring cohort to determine the additional value of apoB beyond LDL-C or non-HDL-C as a predictor of coronary heart disease (Pencina MJ, et al. *Eur J Prev Cardiol.* 2015;22[10]:1321–1327). “We separated the population into tertiles,” he explained. One-third of the population had cholesterol-enriched particles, one-third had cholesterol-depleted particles, and the middle third had an average amount of cholesterol.

LDL-C and apoB are highly correlated variables, Dr. Sniderman said, “but there can be significant discordance,” meaning “that for a specific value of one, there’s a range of values for the other.”

For the bottom tertile of participants, the average apoB was 86.7 mg/dL, and in the top tertile of participants, the apoB was 116 mg/dL, he said, and those who have more apoB have more events. LDL-C levels were nearly the same: 134 mg/dL for the bottom tertile of participants and 136 mg/dL for the top tertile. So the laboratory reporting the result has “reported a biologically false result,” he said, “because they’re not the same in terms of their outcome.”

The same survival result was found for the tertiles of discordant apoB versus non-HDL-C. Average apoB in one tertile was 91.1 mg/dL; non-HDL-C was 159 mg/dL. In the other tertile: apoB, 111 mg/dL; non-HDL-C, 160 mg/dL. People with a high apoB “are in trouble” because they won’t be recognized and treated. “The doctors will be making decisions about giving a drug with inadequate information.”

Dr. Sniderman shared a list of 16 discordance studies, “all of which favor apoB” over LDL-C/non-HDL-C (for example: Kim C-W, et al. *Circ J.* 2021;85[6]:900–907; Johannesen CDL, et al. *J Am Coll Cardiol.* 2021;77[11]:1439–1450; Razavi AC, et al. *Am J Prev Cardiol.* 2021;7:100190). He’s reviewing two additional such studies now. “That’s 18 in a row. That counts as done,” he said.

Even clinical trials favored apoB as the primary CVD marker. “We did a meta-analysis back in 2014, and the bottom line was apoB won,” Dr. Sniderman said, citing one such study (Thanassoulis G, et al. *J Am Heart Assoc.* 2014;3[2]:e000759).

In a Mendelian randomization analysis, Ference, et al., found in some cholesteryl ester transfer protein statin inhibitors, “if you follow the cholesterol, when you used combined therapy, it was wrong,” Dr. Sniderman said. “It didn’t show you the result, whereas the apoB was always true” (Ference BA, et al. *JAMA.* 2017;318[10]:947–956). Ference, et al., concluded: “The clinical benefit of lowering LDL-C levels may . . . depend on the corresponding reduction in apoB-containing lipoprotein particles.” They showed, Dr. Sniderman said, that “every lipid-lowering therapy that has worked tracks apoB” (Ference BA, et al. *JAMA.* 2019;321[4]:364–373).

A Copenhagen-based discordance analysis published last year sought to determine if elevated apoB and/or non-HDL-C are superior to elevated LDL-C in identifying statin-treated patients at residual risk of all-cause mortality and myocardial infarction. The authors found “if the LDL cholesterol is high but the apoB is low, the outcome is good,” Dr. Sniderman said, “whereas if the apoB is high, and the LDL-C is low, the outcome is bad” (Johannesen CDL, et al. *J Am Coll Cardiol.* 2021;77[11]:1439–1450). Citing the study’s data, he added: “A small number of cholesterol-enriched particles is not bad for you. A larger number of cholesterol-depleted particles is. It’s the number of atherogenic particles” that is key, he said.

A study published this year used the population-based UK Biobank and two international clinical trials—Fourier (a PCSK9 inhibitor plus statin) and Improve-It (ezetimibe plus statin)—to look at whether common measures of cholesterol concentration, TG concentration, or their ratio were associated with CVD risk beyond the number of apoB-containing lipoproteins (Marston NA, et al. *JAMA Cardiol.* 2022;7[3]:250–256). “But instead of looking for the c-statistic, they did a head-to-head” comparison, Dr. Sniderman said. In the unadjusted analysis performed for the

clinical factors, he said, non-HDL-C and apoB were equal. “When they’re adjusted for each other, non-HDL becomes nonsignificant and apoB wins.”

Marston, et al., concluded: “In this cohort study, risk of MI was best captured by the number of apoB-containing lipoproteins, independent from lipid content (cholesterol or TG) or type of lipoprotein (LDL or TG-rich). This suggests that apoB may be the primary driver of atherosclerosis and that lowering the concentration of all apoB-containing lipoproteins should be the focus of therapeutic strategies.”

In another study published this year (Odyssey Outcomes), on apoB, residual risk after acute coronary syndrome, and the effects of alirocumab (Praluent), “apoB beats cholesterol and non-HDL cholesterol,” Dr. Sniderman said. In this statin-PCSK9 trial, as in the other, he said, “at baseline and beyond treatment [four months], apoB predicts risk linearly, down to the lower level of detection,” where it’s difficult to measure LDL-C accurately but “you can accurately measure apoB.”

Test	Cost	Total test cost	Other screening costs	Statin costs	Total costs	Test cost/total cost
Lipid panel	13.39	25,354,129	149,722,915	3,229,395,322	3,404,472,366	0.74%
Lipid panel + apoB	34.48	65,280,352	149,722,915	3,229,395,322	3,444,398,590	1.90%

Kohli-Lynch CN, et al. *Clin Chim Acta.* 2020;508:103–108.

Statins reduce cholesterol more than they do apoB, he noted. ApoB is reduced about 75 percent of the amount that LDL cholesterol is, and non-HDL cholesterol is also reduced more than apoB. “This means that when you’re looking at the LDL cholesterol or non-HDL cholesterol, even if you measured it accurately, it’s wrong,” Dr. Sniderman said. “It either overestimates or underestimates,” especially in the case of LDL-C. “You’re not even getting the LDL cholesterol you would get if you were accurately measuring the number of particles.”

The World Health Organization (1994), AACC (2009, 2013), European Society of Cardiology/European Atherosclerosis Society (2019), and European Federation of Clinical Chemistry and Laboratory Medicine/EAS (2020) have all said apoB can be measured rapidly, inexpensively, and more accurately, particularly at low concentrations, than LDL-C and non-HDL-C, and with standardized methods, using automated, widely available assay systems, Dr. Sniderman said. The same groups said the measurements of triglycerides and HDL-C are not standardized and there is inaccuracy and imprecision in their measurements, he said. While there is a consensus approach to harmonizing the results (“and I salute the people who did that,” he said), “no matter how you change the calculation of LDL cholesterol, based on triglycerides and HDL cholesterol, you can’t improve on measurements that weren’t standardized,” he said. “Moreover, in the age of low levels of cholesterol, the error in HDL cholesterol becomes determinative.”

In a study published in 2020 on the clinical utility of apoB versus LDL-C/non-HDL-C, Dr. Sniderman and coauthors wrote, “Adding apoB to clinical care would increase cost trivially” (Kohli-Lynch CN, et al. *Clin Chim Acta.* 2020;508:103–108). In their analysis, the cost of a lipid panel was $13.39 and a lipid panel plus apoB, $34.48 (see **table**). When other screening and statin costs are figured in, the difference in total costs is “trivial,” he said. “This is doing an apoB every single time you do a lipid panel. And I support doing a lipid panel as part of the diagnostic approach to the patient at the beginning, but if you’re following a patient on statin therapy, all you need is apoB.”

Lipoprotein (a), or Lp(a), is a special category of particle and a “particularly poisonous” particle, Dr. Sniderman notes. He uses Lp(a) level as a factor in determining whether to treat apoB because, he says, “if you lower apoB, you will lower the patient’s total risk. And we have found that when the apoB is low, the Lp(a) is not a major risk factor.

“More work needs to be done there, but certainly at the moment,” he continues, “the best therapy for high Lp(a) is a low apoB.”

Whether insurers cover apoB testing depends on what guidelines say, Dr. Sniderman says. “If the guidelines recommended apoB, it would be covered. In fact, a lot of the major insurers already cover apoB, and they do so based on the European guidelines. It’s the American guidelines that are lacking.”

There is no lack of evidence that apoB is better, he insists. “The metabolic studies of the apoB lipoproteins are clear. The pathophysiology of atherosclerosis is clear. The cross-sectional studies that were done [decades ago] were the first evidence, and they turned out to be right.” The prospective observational studies are numerous, and the discordance analyses are definitive, he said. “And now with the Mendelian randomization trials, I think we’re there.

“It is fair to ask for overwhelming proof. But I submit to you there is now overwhelming proof.”

Amy Carpenter Aquino is CAP TODAY *senior editor.*