

CLINICAL LABORATORY STRATEGIES

Mastering Change in Laboratory Practice

Simplifying Cholesterol Screening

Triglycerides and Fasting Unnecessary, Study Says

By Bill Malone

Clinicians typically use fasting levels of total cholesterol, HDL-C, triglycerides, and lab-calculated LDL-C to assess the risk for coronary heart disease. However, a new meta analysis of 68 long-term studies has concluded that lipid assessment should be simplified to either total cholesterol and HDL-C or apolipoproteins—without regard to triglycerides and without asking the patient to fast. This issue of Strategies examines these findings.

Although the message that low-density lipoprotein cholesterol (LDL-C) should be measured and possibly treated with statins is heard loud and clear both in the medical community and through ubiquitous advertising by pharmaceutical companies, uncertainty has surrounded high-density lipoprotein cholesterol (HDL-C) and triglycerides. Similarly, measuring apolipoprotein A1 (apo A1) and apolipoprotein B (apo B) remains controversial as a replacement for HDL-C and LDL-C, respectively.

Now the authors of a super-sized meta-analysis of dozens of studies suggest that labs dethrone the almost 40-year-old Friedewald formula for calculating LDL-C and focus on just HDL-C and total cholesterol (JAMA 2009;302:1993–2000). This new “simplified” testing would include the option of a simple subtraction of HDL-C from total cholesterol to report non-HDL-C instead of LDL-C, and casts aside completely the measurement of triglycerides, and along with it, the need for fasting. The researchers also go a step further, recommending that the choice of using apolipoproteins instead of classic lipids “should hinge on more practical considerations,” such as cost, availability, and standardization of assays.

Emanuele Di Angelantonio, MD, senior research associate in the Cardiovascular Epidemiology Unit at University of Cambridge, U.K., the lead author, and colleagues reviewed data on 302,430 individuals without initial vascular disease from 68 long-term prospective studies in the Emerging Risk Factors Collaboration, mostly in Europe and North America. “The power of this analysis is really that it pulls together so many different studies with almost 3 million person-years,” he said. “Others have usually considered only a single cohort or can be biased by acute events, such as in case-controlled retrospective studies. Ours were all prospective studies with a long follow-up, maximizing the power of size while still being able to analyze a lot of detail.”

Di Angelantonio and his colleagues found that hazard ratios (HRs) with non-HDL-C and HDL-C were nearly identical to apo B and apo A1, and that HRs for vascular disease with lipid levels were at least as strong in participants who did not fast as in those who fasted. HRs were also similar with non-HDL-C as with directly measured LDL-C. Finally, in contrast to previous findings, triglyceride concentration was not independently related with coronary heart disease risk, after controlling for HDL-C, non-HDL-C, and

other standard risk factors, including null findings in women and under non-fasting conditions. The authors concluded that “for population-wide assessment of vascular risk, triglyceride measurement provides no additional information about vascular risk given knowledge of HDL-C and total cholesterol levels, although there may be separate reasons to measure triglyceride concentration (e.g., prevention of pancreatitis),” and that “lipid assessment in vascular disease can be simplified by measurement of either cholesterol levels or apolipoproteins without the need to fast and without regard to triglyceride.”

Getting rid of the requirement to fast could be a major change for patients, clinicians, and labs, according to Di Angelantonio. “For decades, people have been asked to fast overnight for the cholesterol test, and this finding basically says that the cholesterol measurement is just as good in people that fast as those that did not fast,” Di Angelantonio said. “I think this could significantly affect current practice if taken seriously.”

Aside from the inconvenience to patients who fast when asked to, the fasting requirement has been a thorn in the side of labs for years due to the rate of patient non-compliance. For some labs, problems with fasting are one of the biggest reasons for reversing patient charges, explained Daniel Hoefner, PhD, clinical chemist at Marshfield Labs in Marshfield, Wis. Hoefner was not associated with the study. “Often patients tell their doctor after we do the testing that they weren’t fasting. Then we have to reverse the charges and the patient will have to come in and get the blood work done again,” he said. “So to me there are several benefits of not requiring the patient to fast. One is the convenience for the patient themselves, but the other reason is you get a good, valid, accurate result from the non-HDL cholesterol without a fasting sample.”

Though from Hoefner’s view, the study underscores the utility of non-HDL-C over LDL-C by getting rid of the triglycerides used for the calculation, many physicians will continue to expect triglyceride measurement on their lab reports, he predicted. “Perhaps some clinicians will go with just total cholesterol and HDL. But others will want the triglycerides to be able to pick up patients with metabolic syndrome,” he said. “So is this really going to affect screening? It’s a tough question.”

Another factor that could slow adoption of the study’s suggestion for simplified screening comes from how entrenched the focus on LDL has become for regulatory bodies and other groups that influence practice. For example, a pay-for-performance demonstration project initiated by the Center for Medicare and Medicaid Services (CMS) pays bonuses based in part on a healthcare group’s use of LDL-C testing. The quality measures used by the program include LDL-C testing for both diabetes and coronary artery disease care. “Under this program, if a clinic or a hospital tracks how many patients they’re running LDL-C on, if it’s above a certain threshold, it suggests to CMS that it’s a facility that is following their guidelines and therefore they reward them monetarily,” explained Hoefner. “To me, that’s almost one of the bigger issues as opposed to the clinical question of whether you’re doing the patient a better service by suggesting non-HDL-C over LDL-C and triglycerides. The answer might be yes, but some reluctance remains in the institution because there is no reward associated with non-HDL-C over LDL-C.”

Beyond the simplification of cholesterol measurement itself, the study also touches on a hot topic when it suggests that apolipoproteins and classic lipids are essentially interchangeable, admitted Di Angelantonio. “Of course, other studies are needed to confirm this,” said Di Angelantonio. “Also, new analyses are needed to compare the predictive ability of apolipoproteins and standard cholesterol fractions to assess cardiovascular risk. So this study is one step, but not the final one.”

Though the size of this study makes it powerful, in practice, this type of analysis does not sum up all truth for all patient groups, Hoefner cautioned. In fact, many laboratorians and physicians have been looking closely at apolipoproteins to fill in the gaps by the cholesterol-based surrogates for lipoprotein particle numbers (i.e., HDL-C and LDL-C). Though the study found apolipoproteins to be no better or worse than classic lipids, this correlation might not be as tidy for some patients, Hoefner explained. "While you can have a high degree of correlation in this type of study, it doesn't necessarily mean you're going to have a high degree of concordance clinically, especially with sub-populations," he said. "For example, in a sub-group of individuals with insulin resistance or metabolic syndrome, I'm sure there are going to be people who say, this doesn't really work well for those groups of patients. There are still cases where it's the particle number that is going to have much more clinical significance and patients will benefit from an apo B or LDL particle number measurement." Apo B also shows promise in indicating residual risk for patients taking statins to lower LDL-C, he noted.

In the future, this and other such studies will play an important role in pushing clinicians to embrace new approaches to CVD risk, Hoefner said. "I don't think this study radically departs from current knowledge, but since there has been such a tremendous effort now for several decades to focus solely on LDL-C, it seems to be so engrained in medicine today that even a small departure like this is a hard message to get buy in from the clinicians who are using it," said Hoefner. "I really think that in a couple of decades we'll look back at the focus we held onto for so long with LDL-C, and it will be seen as one of the biggest stumbling blocks in cardiovascular disease medicine."