Are Additional Lipid Measures Useful?

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Abstract

Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are the well-established standards by which clinicians identify individuals at risk for coronary artery disease (CAD), yet nearly 50% of people who have a myocardial infarction have normal cholesterol levels. Measurement of additional biomarkers may be useful to more fully stratify patients according to disease risk. The typical lipid panel includes TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs). Emerging biomarkers for cardiovascular risk include measures of LDL-C pattern, size, and density; LDL particle number; lipoprotein(a); apolipoproteins (apoA1 and apoB100 being the most useful); C-reactive protein; and lipoprotein-associated phospholipase A_2. Some of these emerging biomarkers have been proven to add to, or be more accurate than, traditional risk factors in predicting coronary artery disease and, thus, may be useful for clinical decision-making in high-risk patients and in patients with borderline traditional risk factors. However, we still believe that until treatment strategies can uniquely address these added risk factors—ie, until protocols to rectify unhealthy findings are shown to improve cardiovascular outcomes—healthcare providers should continue to focus primarily on helping patients reach optimal LDL-C, HDL-C, and TG levels.

Traditional cardiovascular disease (CVD) risk factors do not fully explain individual or population risk for the development of CVD. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are the well-established standards by which clinicians identify individuals at risk for coronary artery disease (CAD), yet nearly 50% of people who have a myocardial infarction (MI) have normal cholesterol levels.[1] It is desirable for the clinician to more fully stratify patients according to disease risk, while simultaneously being able to offer effective treatments to reduce that risk. Over the past decade, more precise tools for measurement of lipid density—the size and number of lipoprotein particles, markers of inflammation, etc—have been developed in attempts to develop risk-prediction tools, explore new treatments, and better understand the protective benefits of current treatment options. Whether these tools have added value at the present time is the subject of this article.

Decision-making challenges are created because commercial development of laboratory assays to measure emerging risk factors have introduced many of these testing options into the clinical environment. Clinicians want to educate patients and reduce risk as precisely as possible; yet, using novel clinical testing prematurely—ie, before testing has been fully proven to be relevant in risk stratification or before using test results translates into improved clinical outcomes—accrues costs to the general healthcare system and may cause both doctors and patients to avoid research-tested treatments for risk reduction. For example, patients are often nervous about taking proven treatments to lower LDL and instead are excited about taking nutritional supplementation based on the premature use of genetic testing, despite a lack of data based on such genetic testing that show improvements in hard clinical outcomes. Additionally, patients can become attached to conjectures that traditional risk factors are not important, leaving the clinician in the difficult position of trying to explain the importance of controlling traditional risk factors, despite the patient's learned bias against such control; this is a "missing the forest for the trees" phenomenon.

In making the decision whether to test for, and whether to treat based on, emerging risk factors, we recommend the following considerations:

1. Does the test result provide valid, independent information on my patient's cardiovascular risk?
2. Is there unique treatment available for this risk factor that is safe, well researched, and accessible?
3. Will testing and treatment for the risk factor somehow distract me or my patient from addressing his or her risky profile based on well-established risk factors?
4. Does treatment impact hard clinical outcomes, ie, cardiovascular events and death, not just biomarker reduction?

This article reviews the contribution that additional biomarkers make to identifying coronary artery disease (CAD) risk. We have limited this review to biomarkers that are both part of standard laboratory offerings and, when medically appropriate, covered by insurance. In a subsequent article, we will prioritize treatment options according to potential benefit for risk-factor reduction.

Traditional Risk Factors and Treatments

The typical lipid panel includes TC, LDL-C (preferably measured directly rather than calculated), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) (see Table 1).

Table 1. Traditional Lipid Panel and Recommended Treatment Goals for Cardiovascular Disease Prevention[34]		
Total Cholesterol	Desirable (low)	< 200 mg/dL
	Borderline high	200-239 mg/dL
	High	240 mg/dL or greater
HDL Cholesterol	Desirable (high)	> 60 mg/dL
	Acceptable	40-60 mg/dL
	Low	< 40 mg/dL
LDL Cholesterol	Desirable (low)	< 100 mg/dL
	Acceptable	100-129 mg/dL
	Borderline high	130-159 mg/dL
	High	160-189 mg/dL
	Very high	190 mg/dL or greater
Triglycerides	Desirable (low)	< 150 mg/dL
	Borderline high	150-199 mg/dL
	High	200-499 mg/dL
	Very high	500 mg/dL or greater

TC in isolation is of little clinical value, although it is frequently used in combination with HDL for risk stratification. Desired values are low, < 200 mg/dL.

LDL-C, largely because of historical use (since 1885) both clinically and in population research, is still the primary biomarker used to measure cardiovascular risk. It is a measure of the cholesterol content of lipoproteins. Desired values are low, < 100 mg/dL. While we now know that LDL-C is a fairly imprecise marker, it is worth recalling that, by using it, evidence of a causal relationship in the pathogenesis of CAD is shown; patients with homozygous familial hypercholesterolemia, who generally have LDL-C levels of > 500 mg/dL, can experience MI and ischemic death in the first decade of life.[2] Most cholesterol-lowering treatment strategies (such as statins) seem to demonstrate their primary benefit in reducing mortality and cardiovascular events by reducing LDL-C.[3]

Very low-density lipoproteins (VLDLs) are secreted from the liver, transport TGs, and are precursors of LDL-C. VLDLs are overproduced in people with insulin resistance and diabetes.[2] Treatment strategies that reduce fatty infiltration of the liver, including dietary change, physical activity, insulin sensitization, and pharmacologic TG reduction, are appropriate. Achieving desired control of TGs and LDL will lead to desirable VLDL levels, and thus VLDL does not require separate measurement.

HDL-C is involved in reverse cholesterol transport; ie, the transfer of cholesterol from peripheral cells to the liver, to be secreted as bile acids. Desired values are high, > 60 mg/dL. The concentration of HDL-C has a strong inverse relationship to the incidence of CVD. This protective effect is due not only to its promotion of reverse cholesterol transport from vascular walls to the liver, but also to its anti-inflammatory, antioxidant, and antithrombotic effects. When it comes to treatment, niacin is one of few lipid-lowering treatments praised for its ability to raise levels of HDL-C. Clinical trials of niacin have demonstrated reduction of intima-media thickness (IMT) in the vascular wall, suggesting regression of atherosclerotic plaque; this effect appears to be directly correlated with HDL-C concentration.[4]

The independent contribution of TGs to cardiovascular risk remains controversial, mostly due to inconsistent data based on fasting TG levels. Interestingly, 3 recent evaluations in large, population-based cohorts suggest non-fasting TG concentration is an independent risk factor for MI, ischemic heart disease, and cardiovascular-related death.[5-7] Although the exact mechanism for this increased risk is unknown, postprandial hyperlipemia is known to contribute to endothelial dysfunction, an earlier, yet cumulative, step in artherogenesis.[8]

LDL-C and HDL-C: Pattern, Size, and Density

Two patterns predominate and are used to describe the average size of LDL particles. Pattern A refers to a preponderance of large LDL particles, while Pattern B refers to a preponderance of small LDL particles; a minority of individuals displays an intermediate or mixed pattern. Some commercially available assays further subdivide LDL-C into 7 distinct designations based on particle size.[9,10]

Some data suggest that small, dense LDL-Cs are more atherogenic than their large, buoyant counterparts; thus, pattern recognition may allow more-precise risk stratification. Suggested mechanisms of small, dense LDL-C's increased atherogenicity include their increased susceptibility to oxidation, reduced affinity to LDL receptors, and reduced hepatic clearance.[11] In hyperlipemic environments—ie, in individuals with elevated serum TGs and free fatty acids—enzymatic changes to large LDL particles (via cholesteryl ester-transfer protein [CETP]) result in TG-rich, cholesterol-poor, small, dense LDLs. Hence, small, dense LDL particles are known to predominate in a TG-rich environment. Small LDL particles have been shown to be positively associated with non-fasting TGs and inversely associated with HDL-C.[12] In multivariate prediction models, levels of HDL, TGs, and insulin were all independent predictors of small, dense LDL particles.[13] Given these associations with risk factors that clinicians are already routinely measuring, the question becomes: Does LDL-C pattern, as opposed to LDL-C presence only, contribute independently to our assessment of CAD risk?

The 4637-men Quebec Cardiovascular Study found, after adjustment for systolic blood pressure, medication use, and family history, an increased odds ratio of 2.5 (95% CI: 1.2-5.2) for ischemic events in individuals with a small, dense LDL-C pattern.[14] Compared to men in the cohort without ischemic events, the former individuals had significantly lower mean LDL-C size (P<.001) and an increased proportion of very small LDL-C sizes.[15]

The relationship between LDL-C pattern and carotid atherosclerosis (measured by IMT) was also tested in the Multiethnic Study of Atherosclerosis, a cohort of 5538 multiethnic participants, with much different results from those above. After standard adjustments for age, sex, race, hypertension, and smoking, small LDL-particle concentrations, but not large LDL-particle concentrations, were significantly associated with increased

IMT. This finding was similar to other studies. However, when the data were analyzed looking at the relationship between concentration of large LDL within strata of small LDLs, IMT was positively associated with increasing concentrations of both small and large LDL-particle concentration. Said differently, IMT increased with increasing quartiles of small LDL concentration yet also increased with increasing large LDL concentration within each quartile of small LDL. On a per-particle basis in this study, large LDL-Cs actually became more strongly associated with IMT than did small LDL-Cs! This study was the first to control for interclass correlations between particle patterns and thus more precisely describes interclass correlations between lipoprotein particles; it does *not* support a unique association between small LDL particles and atherosclerosis.[16]

Given the proven high correlation between small, dense LDL—ie, Pattern B, with elevated TGs and reduced HDL-C—and given the inclusion of TGs and HDL-C on standard lipid panels, we believe that many clinicians can gather nearly equivalent information to that provided by these newer lipid-density profiles by simply understanding these relationships and using routine lipid tests. That is to say, if a patient has high TGs and low HDL-C, you can assume high numbers of small, dense LDLs just because you understand the effects of TGs on lipoprotein density. In addition, LDL-C remains a driving force in the development of atherosclerosis independent of particle size.

If you haven't already guessed, the inter-relatedness of lipid measurements in cardiovascular risk reduction cannot be ignored. As mentioned, TGs directly impact LDL density and size. TGs also have a similar effect on HDL-C: As with LDL-C, TG-rich HDLs are formed by the action of CETP creating smaller, and more-dense, HDL particles; small, dense HDL particles (HDL-3) are catabolized more quickly from circulation and thus do not remain involved in reverse cholesterol transport from the periphery.[17, 18] In hypertriglyceridemia, the rate of HDL synthesis remains constant while the rate of HDL catabolism increases, resulting in lower quantities of circulating HDL cholesterol.[18] Additionally, several studies have demonstrated that HDL-3 has reduced antioxidant action in its ability to protect LDL cholesterol from oxidation; even in healthy individuals, attenuated antioxidant response was proportional to TG concentration in the HDL particle.[19, 20] Because of these inter-relationships, treating high TGs is paramount to both (1) increasing quantities of HDL cholesterol (by reducing its clearance), and (2) maintaining nonoxidized LDL cholesterol (by maintaining a larger, more-buoyant HDLpattern).

LDL Lipoprotein Particle Number

LDL particle number (LDL-P) is a measure of the number of lipoprotein particles independent of the quantity of lipid within the cholesterol particle; ie, LDL-P measures the number of individual particles, not a concentration like LDL-C. It is measured using nuclear magnetic resonance technology and is unaffected by fasting status.[21] Higher LDL-P measures have been associated with a higher risk of CAD. This might simply be because there are more particles susceptible to oxidation in circulation.* There are suggestions, but not definitive proof, that reducing LDL-P increases intra-LDL antioxidant capacity.

The European Prospective Investigation of Cancer (EPIC)-Norfolk cohort, a study that has followed 25 663 participants (men and women aged 45-79 years) over 6 years, evaluated associations between LDL-P and risk of CAD. Compared to controls, cases of CAD had a higher number of LDL particles (LDL-P $P<.0001$), smaller average LDL-particle size ($P=.002$), and higher concentrations of small LDL particles ($P<.0001$).[22] Once again, small, dense LDL-C were positively associated with TG and negatively associated with HDL.

In another study investigating incident angina and MI with LDL-P, females, but not males, had a significantly increased odds ratio for incident MI and angina for higher LDL-P—but not for LDL size—after adjustment for LDL, age, and race. Males had increased (but not significant) point estimates showing the same relationship.[23] Of note, LDL-P and non-HDL-C (ie, TC minus HDL-C, or, specifically, LDL-C plus VLDLs), added equivalently to Framingham-predicted CAD risk stratification, thus reducing our enthusiasm for this additional measurement when TC and HDL-C are routinely available.[22]

Based on these results, LDL-P is becoming recognized as a more-precise measure of LDL-related risk and, as it becomes more available, is likely to replace LDL-C in risk-stratification tools. Clinical availability is currently limited; however, Medicare recently began reimbursing for regular testing of LDL-P in high-risk patients, so we should see availability increase soon. There are no novel treatments based on LDL-P at this time, and data shows therapies that lower LDL-C lower LDL-P as well.

Apolipoproteins

Apolipoproteins are the protein components of plasma lipoproteins. Several different apolipoproteins have been identified and numbered; however, apoB48, apoB100, and apoA are the most commonly referenced.

ApoB48 is associated with LDL particles that transport dietary cholesterol to the liver for processing. ApoB100 is found in lipoproteins originating from the liver (eg, LDL and VLDL); it transports these lipoproteins and, also, TGs to the periphery. In addition, ApoB100 is involved with the binding of LDL particles to the vascular wall, implicating itself as a key player in the development of atherogenic plaques. Importantly, there is one apoB100 molecule per hepatic-derived lipoprotein. Hence, it is possible to quantify the number of LDL/VLDL particles by noting the total apoB100 concentration.

Measurement of apoB100 has been shown in nearly all studies to outperform LDL-C and non-HDL-C as a predictor of CAD events and as an index of residual CAD risk, perhaps due to differences in measurement sensitivity between measurement methodologies. Direct measurement of apolipoproteins is superior to calculated lipid measurements. Yet, currently, apoB100 measurement is more costly than routine measurements and, because apoB100 is so closely associated with non-HDL-C (which,

*Authors' Note: We use the analogy of bullets in a revolver. The more bullets (LDL-P) in the chamber (blood), the more likely the gun will fire (will oxidize) when you pull the trigger (make less-optimal dietary choices).

as mentioned previously, can be estimated by TC minus HDL-C), our enthusiasm for the clinical use of this test is limited.[24]

For its part, apoA is associated with HDL particles; the 2 major proteins in HDL are apoAI and apoAII. Of these, apoAI has more frequently been used to estimate HDL-C, but, in contrast to apoB100, apoAI is not unique to HDL and so the ratio of apoAI to HDL is not 1 to 1.[24]

Recently, it has been suggested that the apoB100:apoAI ratio be widely adopted as a risk marker or treatment target. Several large epidemiological studies strongly support this concept by finding the apoB100:apoAI ratio to be superior to lipoprotein measurements as a risk marker.[25] However, important questions remain. For example, is a high ratio caused by low apoAI equivalent to a low ratio caused by high apoB100? And how would treatment goals be made without the unique information contributed by the apoB100/LDL component in comparison to the apoAI/HDL? These questions do not have definitive answers, although the role of HDL in reverse cholesterol transport—and in maintaining a reduced (not oxidized), state of LDL—suggests that risks of elevated LDL can be offset by increased HDL (yet risk would be even further reduced if LDL were lower, and thus the ratio of apoB100:apoAI were lower).

It is critically important to note the values of apoB100:apoAI and the corresponding TC:HDL ratio that appear to be protective. According to INTERHEART, a large, case-controlled study in almost 30 000 patients across 52 countries, the average apoB100:apoAI ratio of ~0.8 (and corresponding TC:HDL ratio of ~5.0) carries a 2-fold relative risk of MI compared to those participants with an apoB100:apoAI ratio of 0.43 (and corresponding TC:HDL ratio of 2.7). Risks predicted by apoB100:apoAI were consistently *greater* than risks predicted by the corresponding ratio of TC:HDL down to an apoB100:apoAI ratio of 0.6 (and corresponding TC:HDL ratio of 3.8), where the apoB100:apoAI ratio and TC:HDL ratio predict equivalent risk.[26, 27]

This information makes it tempting to rapidly incorporate an apoB100:apoAI ratio into practice; however, estimates of apoB100:apoAI ratio risk run nearly parallel with risk predicted by the TC:HDL ratio, with apoB100:apoAI predicting greater risk, until the apoB100:apoAI reaches 0.8, where they diverge more sharply. What does this mean? And how does it relate to what to use in practice? The point is that if you are reducing the TC:HDL ratio, you are also reducing the apoB100:apoAI ratio, and, until you reach a TC:HDL ratio of < 2.7, your patient remains at increased risk. In addition, if your patient's TC:HDL ratio is > 2.7, were you to measure their apoB100:apoAI ratio, their risk will be even greater than that predicted by TC:HDL. So, clinically, a practitioner should focus on reducing the TC:HDL ratio first, and then fine tune if desired—ie, only at that point ordering a single apoB100:apoAI ratio to confirm optimal risk reduction. Some example scenarios of TC:HDL ratio = 3.0 (for ease) would be: TC = 220, HDL = 73, thus non-HDL = 147; TC = 200, HDL = 67, thus non-HDL = 133; TC = 150, HDL = 50, thus non-HDL = 100. Until you reach these targets, we wouldn't recommend ordering more-expensive testing. However, if you have access to apoB100:apoAI testing at a comparable cost to your patients, then it is reasonable to use. One final note: Although clinical outcomes based on a reduction of the apoB100:apoAI ratio are expected to follow risk reductions based on a TC:HDL reduction, this has not been demonstrated in prospective trials.

Lipoprotein(a)

Lipoprotein(a)—Lp(a)—is attached to apoB. The association of Lp(a) with CAD and its ability to act as a biomarker of risk appears to be strongest in patients with hypercholesterolemia and, in particular, in young patients with premature atherosclerosis (males younger than 55 and females younger than 65). Part of the reason for this is the observation that there seem to be important threshold effects such that only very high Lp(a) levels (> 30 mg/dL) are associated with elevated vascular risk; in this regard, these increased plasma levels of Lp(a) independently predict the presence of CAD, particularly in patients with elevated LDL-C levels.[28]

In the Cardiovascular Health Study, a relative risk of approximately 3-fold for death from vascular events and stroke was seen in the highest quintile compared to the lowest quintile of Lp(a) but for males only, whereas no such relation existed for women.[29] Lp(a) is commonly considered a marker for familial hypercholesterolemia. Lp(a) may best be used in assessing the risk of younger males with strong family histories of CVD but should not be used more generally.

Other Markers

C-reactive protein

While it is perhaps incongruous to include highly sensitive C-reactive protein (hsCRP), a measure of inflammation, in a review of lipoproteins, we feel it worth brief mention because atherosclerosis does not occur solely as a result of the quantity and quality of lipids in the body. It is generally known that hsCRP provides a stable plasma biomarker for low-grade systemic inflammation. It is produced predominantly in the liver as part of the acute phase response; however, hsCRP is also expressed in smooth muscle cells within diseased atherosclerotic arteries. Elevated hsCRP represents the culmination of numerous proinflammatory pathways and has been implicated in "multiple aspects of atherogenesis and plaque vulnerability, including expression of adhesion molecules, induction of nitric oxide, altered complement function, and inhibition of intrinsic fibrinolysis."[2]

In a large 10-year cohort study, the relative risk of cardiac death was doubled with increasing hsCRP quartiles. Patients in the top quartile (with a mean hsCRP of 4.2 mg/dL) had 6 times increased risk compared to the lowest quartile (mean hsCRP of 1.20 mg/dL).[30]

In addition to lowering LDL-C, hsCRP reduction has been hypothesized as an additional mechanism of protection by statin-class lipid-lowering drugs; however, this relationship has not been shown convincingly. Currently, a large multicenter clinical trial (named Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin, or JUPITER) is currently attempting to tease apart the contribution

that lowering CRP has on risk-reduction in patients who have elevated hsCRP but not elevated traditional risk factors. Keep your eye out for future mention in the mainstream literature.

Lipoprotein-associated phospholipase A_2

Also called platelet-activating factor acetylhydrolase, lipoprotein-associated phospholipase A_2 (Lp-PLA_2) oxidizes phospholipids, producing a free, oxidized fatty acid and lysophosphatidylcholine—both proinflammatory molecules. It exists primarily on LDL particles but also occurs on HDL and in macrophages.[31] Although Lp-PLA_2 traditionally has been considered a biomarker for stroke risk, it may have more clinical utility for general cardiovascular risk than previously thought: The inflammatory cascade initiated by Lp-PLA_2 appears to be ameliorated by such agents as COX-2 and the fibrate drug gemfibrozil, the use of which may provide clinicians with additional treatment strategies by which cardiovascular risk could be reduced.[32,33] In addition, the potential benefit of antioxidant therapy would be a useful area of research.

The Big Picture

In our efforts to provide the best possible care both for patients with established CVD (high risk) and for those interested in CVD prevention without traditional risk factors (low risk), it is critical first to recognize the contribution of non-lipid CVD risk factors to risk prediction (age, smoking, diabetes history, family history of premature CVD, TC, blood pressure, LDL-C, and HDL-C) and treat to appropriate targets (see Table 2). Relatively rapid risk-prediction tools for use in primary care have been published and can be found online (www.nhlbi.nih.gov/health/prof/other/index.htm).[34] To make the point again, additional testing on emerging risk factors should not substitute for accurate risk prediction and treatment based on established risk factors. With this in mind, a reasonable question to ask is when should additional testing be recommended?

Table 2. Risk Factors for Cardiovascular Disease (Exclusive of LDL Cholesterol)[34]

Cigarette smoking
Hypertension (BP > 140/90 mmHg or on antihypertensive medication)
Low HDL cholesterol (< 40 mg/dL)
Family history of premature CHD (CHD in first-degree male relative < 55 years; CHD in first-degree female relative < 65 years)
Age (men > 44 years; women > 54 years)
Clinical coronary heart disease, symptomatic carotid artery disease, peripheral arterial disease, or abdominal aortic aneurysm

Triglycerides: Technically, TGs are not included in traditional risk calculations, although recent evidence suggests that non-fasting TGs may impact risk, and, as mentioned, hypertriglyceridemia and low HDL-C predict LDL-density patterns; therefore, measurement of TGs in patients with low HDL-C may affect the clinician's choice of lifestyle recommendations. This approach—simply measuring TGs—is also considerably less costly than LDL-C density-pattern measurement.

LDL-C Pattern, Size, and Density: Measurements of LDL-C pattern, size, and density have not convincingly demonstrated unique contributions to cardiovascular risk prediction or, for that matter, to atherogenicity. In fact, as mentioned above, recent analysis refutes the claim of increased atherogenicity of small, dense particles. This conclusion, in combination with high correlations between LDL pattern and levels of HDL and TGs (ie, routinely measured risk factors), led to our deduction that there is limited rationale for ordering these tests, which can be very expensive and confusing for patients.

LDL Lipoprotein Particle Number: Given the lack of novel treatments based on LDL-P and the high correlation between LDL-C and LDL-P, it is difficult at this time to recommend routine LDL-P testing. However, it may provide a useful independent assessment of CVD risk when treatment decisions are unclear (ie, with high LDL-C in the presence of high HDL-C, or borderline LDL-C in the presence of non-LDL risk factors).

Apolipoproteins: Because apoB100 is highly correlated with LDL and VLDL (and therefore with TGs), once again it is difficult to justify apoB measurement as a substitute for, or an addition to, routine lipid measurements.

Lipoprotein(a): Measurement of Lp(a) should be reserved for the young, male patient with a family history of significant CVD (eg, familial hypercholesterolemia) and/or the patient with premature CAD (males younger than 55 and females younger than 65).

C-reactive protein: The hsCRP marker is not currently included in risk-prediction calculators. However, we believe that hsCRP provides critical information on vascular inflammatory burden, a concept now greatly recognized and understood by most patients, and that it can be used clinically to motivate patients toward smoking cessation and lifestyle change. It is important to note that high levels of hsCRP add to risk from elevated LDL-C and/or low HDL-C; low hsCRP does not reduce, or supersede, the risk associated with elevated LDL-C.

Lipoprotein-associated phospholipase A_2: It appears that Lp-PLA_2 can provide useful information for clinical decision-making because it can be lowered with treatment strategies such as cyclooxygenase inhibitors and second-line lipid-lowering agents such as gemfibrozil that may not be considered for reducing LDL-C.[31, 33]

Conclusion

In the United States, treatment guidelines for high CVD risk factors are set by the National Cholesterol Education Program (NCEP) Expert Panel, which developed the third report of the Adult Treatment Panel (ATPIII).[34] Treatment goals are determined according to risk stratification by LDL-C and by known additional risk factors such as smoking, low HDL, hypertension, family history, and age. Yet, clinically, decision-making is always more complex than this. Additional risk stratification can be accomplished by measuring the biomarkers discussed above, and this may potentially provide additive benefit beyond NCEP guidelines. However, we always encourage clinicians to treat known risks to goal levels before adding additional goals for treatment. In a future article we will provide further detail on treatment options for novel biomarkers.

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