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FPIN's Clinical Inquiries

Which Lipoprotein Measurements Are Clinically Useful?

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Clinical Question

Are lipoprotein measurements other than total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides ever clinically useful?

Evidence-Based Answer

Emerging lipid risk factors for cardiovascular disease include lipoprotein remnants, lipoprotein (a), small LDL particles, HDL subspecies, apolipoprotein B, apolipoprotein A-I, and oxidized LDL. Measurement of these levels should not be used for routine cardiovascular risk screening. (Strength of Recommendation [SOR]: C, based on expert opinion and lack of clinical outcomes trials)

An elevated lipoprotein (a) level could be counted as an additional risk factor to justify aggressive LDL lowering in high-risk patients. (SOR: C)

Apolipoprotein B could be used to identify patients at higher risk of fatal myocardial infarction who have lipid abnormalities but normal or low LDL cholesterol levels. (SOR: B)

Evidence Summary

Major risk factors for cardiovascular disease are age, family history of premature coronary artery disease, smoking, hypertension, diabetes, low HDL cholesterol, and elevated LDL cholesterol.¹ However, these traditional risk factors do not predict all future cardiovascular events.¹ Emerging lipid risk factors are being examined to determine if measuring them can improve cardiovascular risk assessment. The current literature on this topic includes two clinical guidelines,^{1,2} a meta-analysis of lipoprotein (a) as an independent risk factor for cardiovascular disease,³ a prospective

cohort study comparing lipoprotein (a) with traditional risk factors for cardiovascular disease,⁴ and a prospective cohort study linking elevated apolipoprotein B to fatal myocardial infarction.⁵

The National Cholesterol Education Program (NCEP) and the U.S. Preventive Services Task Force (USPSTF) both have published guidelines discussing lipid screening.^{1,2} NCEP has a lengthy and detailed discussion of emerging lipid risk factors in its final report. The report discusses lipoprotein remnants, lipoprotein (a), small LDL particles, HDL subspecies, apolipoprotein B, and apolipoprotein A-I and concludes that none of these are appropriate for routine screening. However, it states that an elevated lipoprotein (a) measurement may justify a lower LDL goal in high-risk patients. The report notes that apolipoprotein B may be superior to LDL for cardiovascular risk prediction, but there is not enough evidence for it to replace LDL as a therapeutic target.

The USPSTF states that the evidence supporting the use of lipoprotein (a) is inconsistent and recommends additional study.²

A meta-analysis of 5,436 patients followed for at least one year concluded that elevated lipoprotein (a) is associated with increased cardiovascular risk (relative risk [RR] = 1.6; 95% confidence interval [CI], 1.4 to 1.8).³

A prospective cohort study comparing elevated lipoprotein (a) with traditional risk factors concluded that an elevated lipoprotein (a) level conferred additional risk in patients with hypertension (RR = 3.0; 95% CI, 1.4 to 6.6), elevated LDL (RR = 2.6; 95% CI, 1.2 to 5.7), and low HDL (RR = 8.3; 95% CI, 2.0 to 35.5).⁴ Conversely, the study found no additional risk in patients without these traditional risk factors.

A large prospective cohort study of 175,553 Swedish men and women followed over an average of more than five years examined the cardiovascular risk of elevated apolipoprotein B levels and concluded that apolipoprotein B was strongly and positively related to increased risk of fatal myocardial infarction when controlled for age, total cholesterol, and triglycerides (men: RR = 1.33; 95% CI, 1.17 to 1.51; women: RR = 1.53; 95% CI, 1.25 to 1.88).⁵ Apolipoprotein B also was found to be a stronger predictor of fatal myocardial infarction than LDL cholesterol, particularly in patients with normal or low concentrations of LDL cholesterol.

Although there is mounting support for the association of lipoprotein (a) and apolipoprotein B with cardiovascular disease, there are no data to suggest that more aggressive risk factor modification would improve patient-oriented health outcomes. It is very difficult to modify lipoprotein (a). Some studies suggest that it can be lowered using high doses of niacin, neomycin, or estrogen in women.⁶ Apolipoprotein B can be modified with statins; however, there is not enough evidence to conclude that it is a better clinical marker of cardiovascular risk when compared with LDL cholesterol levels, except in the situations noted above.

Recommendations from Others

NCEP recommends against using lipoprotein remnants, small LDL particles, HDL subspecies, or apolipoproteins for routine cardiovascular risk screening.¹ The guidelines do not discuss the use of oxidized LDL, but they accept lipoprotein (a) screening as an option for select patients.¹

USPSTF does not recommend using lipoprotein (a) for cardiovascular risk screening.²

Clinical Commentary

LDL cholesterol is the primary target of dyslipidemia management. There is conclusive evidence that lowering LDL cholesterol reduces cardiovascular risk, particularly in high-risk patients. Other lipoproteins are, at best, marginally beneficial risk markers. In our practice, we consider measuring additional lipoproteins only for patients who have already attained their LDL cholesterol goal and in whom additional risk stratification is desired. Considering the fact that most patients in the United States are not at their recommended LDL cholesterol goal, the benefits of LDL cholesterol lowering should never be overlooked by false hopes that additional markers may provide further clinical insight. Lower LDL cholesterol goal values are recommended by the NCEP Adult Treatment Panel 2004 update as therapeutic options in two groups of patients: (1) those with LDL cholesterol lower than 70 mg per dL (1.80 mmol per L) who have very high cardiovascular risk (e.g., patients with diabetes and known heart disease); and (2) those with LDL cholesterol lower than 100 mg per dL (2.60 mmol per L) who have high cardiovascular risk.⁷ The need to measure additional lipoprotein markers should be rare.

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