Apolipoproteins for Cardiovascular Risk Assessment

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Clinical Question

Is measurement of apolipoproteins better than traditional lipid measurements for predicting cardiovascular risk?

Evidence-Based Answer

Measurement of apolipoprotein B and apolipoprotein A-I is no better than traditional lipid measurements and should not be used to predict cardiovascular risk. (Strength of Recommendation: B, based on meta-analyses with conflicting results.) Apolipoprotein B and non–high-density lipoprotein cholesterol (HDL-C) predict cardiovascular risk slightly better than low-density lipoprotein cholesterol. Elevated levels of apolipoprotein A-I predict a lower risk of cardiovascular events except stroke, but not as well as elevated HDL-C levels.

Evidence Summary

Apolipoproteins are structural components of lipoproteins and have a role in receptor binding and enzyme activation. Apolipoprotein B is carried on all proatherogenic lipoproteins in a 1:1 ratio, and apolipoprotein A-I is found on nearly all HDL particles.[1]

High levels of apolipoprotein B predict cardiovascular risk about as well as non–HDL-C. A 2012 meta-analysis pooled data from prospective cohort studies of patients without baseline cardiovascular disease and found that non–HDL-C and apolipoprotein B levels were similarly predictive of fatal and nonfatal cardiovascular events[2] *(Table 1[2-4])*. Using a clinical model, the authors calculated that substituting total cholesterol and HDL-C measurements with apolipoprotein A-I and B measurements diminished risk prediction by 1% (95% confidence interval [CI], 0.2% to 1.9%), whereas adding them did not significantly improve risk classification. A 2011 meta-analysis of prospective cohort and case-control studies found that apolipoprotein B was a slightly better predictor of cardiovascular risk than non–HDL-C, and both were superior to low-density lipoprotein cholesterol.[3]

Among patients receiving statins, measurement of apolipoprotein B is comparable to that of non–HDL-C. A 2012 meta-analysis of randomized controlled trials of patients on statin therapy found that time to the first major cardiovascular event was most strongly associated with non–HDL-C levels, followed by apolipoprotein B and low-density lipoprotein cholesterol levels.[4] The differences between hazard ratios were small but statistically significant ($P = .002$ for non–HDL-C vs. low-density lipoprotein cholesterol, and $P = .02$ for non–HDL-C vs. apolipoprotein B).

The benefits of measuring apolipoprotein B include the ability to use serum from nonfasting patients, standardization, and direct measurement compared with the calculated measurement of low-density lipoprotein cholesterol, which may be inaccurate in patients with hypertriglyceridemia.[5,6]

Elevated apolipoprotein A-I levels predict coronary events except stroke, but not as well as elevated HDL-C levels. Apolipoprotein A-I levels are inversely associated with cardiovascular disease. In the 2012 meta-analysis discussed previously, comparable inverse associations for cardiovascular risk were seen with HDL-C and apolipoprotein A-I measurements.[2] A 2011 prospective cohort study of healthy women found an inverse relationship between apolipoprotein A-I levels and the incidence of stroke and coronary events

Table 1. Summary of Meta-analyses Comparing Apolipoproteins vs. Traditional Lipid Measurements for Predicting Adverse Cardiovascular Events

Number and type of studies	*Outcomes measured*	*Adverse events*	*Biomarker measured*	*Risk of elevated biomarker (95% CI)*
26 prospective cohort trials (N = 139,581)[2]	Fatal and nonfatal coronary artery disease and stroke	12,234	Non–HDL-C	HR = 1.27 (1.22 to 1.33)*
			Apolipoprotein B	HR = 1.24 (1.19 to 1.29)*
			Apolipoprotein A-I	HR = 0.87 (0.84 to 0.90)*
			HDL-C	HR = 0.83 (0.78 to 0.87)*
12 (8 prospective cohort and case-control studies; N = 233,455)[3]	Fatal and nonfatal ischemic cardiovascular events	22,950	Apolipoprotein B	RR = 1.43 (1.35 to 1.51)†
			Non–HDL-C	RR = 1.34 (1.24 to 1.44)†
			Low-density lipoprotein cholesterol	RR = 1.25 (1.18 to 1.33)†
8 randomized controlled trials (N = 38,153)[4]	Fatal or nonfatal myocardial infarction, fatal coronary artery disease, hospitalization for unstable angina, and fatal or nonfatal stroke at 1 year	6,286	Non–HDL-C	HR = 1.16 (1.12 to 1.19)*
			Apolipoprotein B	HR = 1.14 (1.11 to 1.18)*
			Low-density lipoprotein cholesterol	HR = 1.13 (1.10 to 1.17)*

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; RR = relative risk.

**—HR is calculated as the increased or decreased risk of an adverse event per standard deviation increase in the biomarker.*

†—*RR is calculated as the increased risk of an adverse event per standard deviation increase in the biomarker.*

Information from references 2 through 4.

(myocardial infarction, coronary revascularization, or coronary death).[7] Participants included health care professionals 45 years and older who were not receiving lipid-lowering therapy and had a low risk of cardiovascular disease. They were grouped into quintiles based on apolipoprotein A-I or HDL-C levels. The average follow-up was 11.1 years. There were 319 strokes and 602 coronary events among the 26,881 women. Lower apolipoprotein A-I and HDL-C levels were associated with a higher risk of coronary events except stroke. However, in all quintiles the coronary event association with apolipoprotein A-I was weaker than that of HDL-C (hazard ratio for apolipoprotein A-I [lowest vs. highest quintiles] = 1.58 [95% CI, 1.14 to 2.20]; hazard ratio for HDL-C [lowest vs. highest quintiles] = 2.19 [95% CI, 1.51 to 3.19]).[7]

Recommendations from Others

The American College of Cardiology Foundation/American Heart Association and the National Academy of Clinical Biochemistry recommend against measurement of apolipoproteins or any additional lipid parameters beyond a standard fasting lipid panel for global cardiovascular risk assessment.[8,9]

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Air Force Medical Service or the U.S. Air Force at large.

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