Reviews

Apolipoprotein Measurements: Is More Widespread Use Clinically Indicated?

Address for correspondence:
Michael H. Davidson, MD, FACC
Department of Internal Medicine
B 308 Clinical Center
Michigan State University
East Lansing, MI 48824-1313
michaeldavidson@radiantresearch.com

Michael H. Davidson, MD, FACC

Preventive Cardiology Center, University of Chicago Pritzker School of Medicine, Chicago, Illinois

ABSTRACT

Apolipoprotein (apo) B may be a more sensitive measure of atherogenicity than low-density lipoprotein cholesterol (LDL-C) and a better index for assessing cardiovascular risk. The refined risk assessment provided by apo B may be important in patients at high cardiometabolic risk such as those with diabetes mellitus or metabolic syndrome, as these conditions are often associated with normal LDL-C values but increased numbers of small, dense low-density lipoprotein (LDL) particles (indicating increased levels of apo B). Although apo B is not currently a treatment target in the United States cholesterol-lowering guidelines, a consensus conference endorsed by the American Diabetes Association and the American College of Cardiology recently recommended that apo B be added as a therapeutic target in patients at high cardiometabolic risk and in patients with clinical cardiovascular disease or diabetes. Suggested target goals are <90 for high risk and <80 mg/dL for highest risk patients. Current clinical data indicate that intensive statin therapy can lower apo B to meet this aggressive goal. While the proatherogenic/antiatherogenic ratio of apo B/apo A-I is a better risk discriminator than the single proatherogenic measurement (apo B), clinical trial data are lacking regarding the impact of increasing apo A-I and high-density lipoprotein on outcomes.

Introduction

Significant risk for cardiovascular disease (CVD) often remains after elevated low-density lipoprotein cholesterol (LDL-C) levels have been treated to goal.[1] This so-called residual risk is particularly problematic in patients with diabetes mellitus or metabolic syndrome, who often have more complex lipid abnormalities than do insulin-sensitive individuals.[1] Since the dyslipidemia associated with insulin resistance—high triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), and small, dense low-density lipoprotein (LDL) particles—is exceptionally atherogenic, optimal CVD risk reduction in diabetic or metabolic syndrome patients likely requires even more accurate risk assessment and focused treatment. Evidence suggests that apolipoprotein (apo) B and apo A-I predict CVD risk more accurately than conventional lipid measures, either separately or together as a calculated apo B/apo A-I ratio. Recent clinical trial data indicate that intensive statin therapy produces significant improvements in these parameters. Although the predictive value of apo B vs non-HDL-C is of great interest, it has recently been reviewed[2] and is beyond the scope of this article, which addresses apo B and apo A-I as risk discriminators compared with LDL-C.

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What Are Apo B and Apo A-I?

Apo B, the structural protein for the atherogenic lipoproteins (very-low-density lipoprotein [VLDL], intermediate-density lipoprotein [IDL], and both large, buoyant LDL and small, dense LDL), is responsible for transporting lipid from the liver and gut to peripheral tissues.[3,4] Each lipoprotein particle contains 1 apo B molecule; therefore, the total apo B level corresponds to the total number of atherogenic particles and denotes the atherogenic potential of the whole lipoprotein fraction (Figure).[4,5] By contrast, apo A-I is the major structural protein for high-density lipoprotein (HDL), and reflects the atheroprotective side of lipid metabolism.[4] Apo A-I is produced both in the liver and intestine and is responsible for initiating reverse cholesterol transport, whereby excess cholesterol in peripheral tissues is carried back to the liver for excretion.[3,4,6]

Although not yet widely measured or used in general clinical practice even though standardized commercial assays exist, apo B potentially could provide a number of methodological advantages over LDL-C (and even non-HDL-C) as an index of CVD risk, including accuracy when measured in the nonfasting state and the ability for direct measurement rather than via calculation of other parameters.[2] Results from 2 major population studies have shown nearly identical distribution of apo B and apo A-I values, despite differences in methodologies, suggesting that measurements

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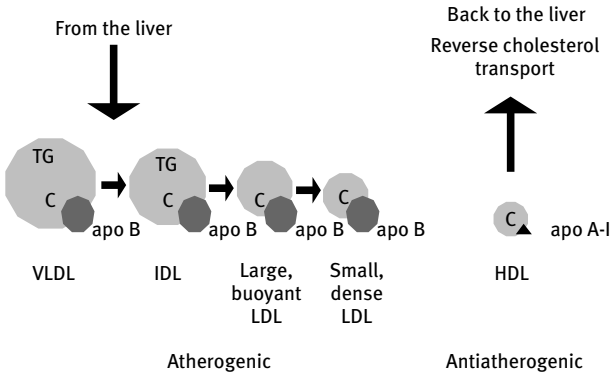

Figure. Atherogenic/antiatherogenic balance between apo B containing particles and apo A-I containing particles. Because there is only 1 apo B particle in the spectrum of VLDL to IDL to LDL, the total apo B level represents the total number of potentially atherogenic particles. By contrast, apo A-I is the major structural protein for high-density lipoprotein (HDL) and is responsible for initiating reverse cholesterol transport. Abbreviations: apo, apolipoprotein; C, cholesterol; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein. Reprinted with permission from Walldius and Jungner.[4]

of these apolipoproteins can be performed with a high degree of accuracy and precision.[7–9] Moreover, the reliability and reproducibility of assays for apo B are comparable to those expected for calculated non-HDL-C.[10] Currently, Canadian guidelines on dyslipidemia management recommend a goal for apo B (<90 mg/dL in high risk patients).[11] An international panel of experts suggested a lower target (<80 mg/dL) and recommended that apo B be adopted as an alternative to both LDL-C and non-HDL-C, which is a measure of all the cholesterol in atherogenic lipoproteins and a secondary target of lipid-lowering therapy.[2,5] Most recently, a Consensus Conference Report from the American Diabetes Association and the American College of Cardiology suggested that measurement of apo B be added to measures of LDL-C and non-HDL-C in patients at high cardiometabolic risk, with target apo B levels set at <90 mg/dL in high risk patients and <80 mg/dL in highest risk patients (Table 1).[12] This recommendation would encompass patients with clinical CVD or diabetes plus 1 or more cardiometabolic risk factors beyond dyslipidemia (ie, at highest cardiometabolic risk) and patients with diabetes and no other risk factors or patients without diabetes or clinical CVD but with 2 or more CVD risk factors (ie, at high cardiometabolic risk).[12]

Rationale for Using Apo B and Apo A-I in Risk Assessment

Cardiovascular risk is more directly related to the number and size of circulating atherogenic particles than to the concentration of cholesterol in these particles.[2,13] Although LDL-C is not typically elevated in the metabolic syndrome, it is highly atherogenic because of the increased presence

Table 1. Suggested Treatment Goals for LDL-C, Non-HDL-C, and Apo B in Patients with Cardiometabolic Risk and Lipoprotein Abnormalities

	Goals (mg/dL)		
Patient Risk Status	LDL-C	Non-HDL-C	Apo B
Highest risk[a]	<70	<100	<80
High risk[b]	<100	<130	<90

[a]Those with (1) known cardiovascular disease or (2) diabetes plus ≥ 1 additional major risk factor (smoking, hypertension, or family history of premature coronary artery disease).
[b]Those with (1) no diabetes or known clinical cardiovascular disease but ≥ 2 additional major risk factors or (2) diabetes, but no other risk factors. Adapted with permission from Brunzell et al.[12]
Abbreviations: apo B, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

of small, dense LDL particles.[13] Therefore, measuring only the LDL-C can underestimate the true atherogenic burden.[13] Measurements of apo B are more accurate, as they quantify the total number of potentially atherogenic particles in plasma. The finding of elevated apo B in a person with a "normal" LDL-C level likely indicates an increased cardiovascular risk.[3,4] Apo B may also be a more important index than LDL-C in patients with atherogenic dyslipidemia since it is disproportionately higher in persons with high triglyceride levels.[13]

By contrast, patients with low levels of apo A-I (<120 mg/dL) are more likely to have CVD than those with high apo A-I levels (≥160 mg/dL).[8] As with LDL, the cholesterol content of HDL particles varies across patient types and is influenced by plasma triglyceride levels[3]; patients with high triglycerides tend to have low apo A-I levels.[3,6] Nonetheless, it is unclear whether apo A-I alone is a predictor of CVD risk independently of its association with HDL.[8] Apo A-I may be most useful in conjunction with apo B in assessing the balance between atherogenic and atheroprotective cholesterol transport, as determined by the apo B/apo A-I ratio.[4] A higher ratio means more cholesterol is circulating in plasma and is more likely to be deposited in arteries, leading to atherosclerosis and a higher risk of CVD events.[4]

Value of Apo B as a Risk Predictor

In the Quebec Cardiovascular Study, lipid and lipoprotein measurements from more than 2000 men free of coronary heart disease (CHD) at baseline showed that elevated apo B was associated with a relative risk of 1.4 of developing CHD over 5 years.[14] Data from 13-year follow-up also showed that a preponderance of small, dense LDL particles was associated with a high short-term risk of CHD, whether or not apo B levels were elevated (relative risk [RR]: 2.1 and 1.9, respectively).[15] However, the combination of small, dense LDL particles and elevated apo B levels was associated with the highest short-term risk (RR: 3.1; $P<.001$).[15] Moreover, apo B appeared to modulate the risk of CHD associated with

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elevated LDL-C. Men with high LDL-C, but low apo B levels did not have an elevated risk of CHD, whereas those with high LDL-C and high apo B had a 2-fold increased risk.[16]

These findings are supported by results of the Apolipoprotein-related Mortality Risk (AMORIS) study, which showed that apo B was strongly and positively related to increased risk of fatal myocardial infarction (MI).[17] Data from the Insulin Resistance Atherosclerosis Study showed that apo B is more closely associated with abdominal obesity, hyperinsulinemia, and other features of insulin-resistant states (such as metabolic syndrome) than LDL-C.[18] Among postinfarction patients with metabolic syndrome, out of 17 laboratory parameters including total cholesterol, HDL-C, triglycerides, and apo A-I, only apo B significantly and independently predicted CVD risk.[19]

Further evidence of the prognostic value of apo B comes from post hoc analyses of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),[20] the Cholesterol and Recurrent Events (CARE) trial,[21] and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial.[22] Overall, these studies have shown that on-treatment apo B is a more reliable measure of residual risk than on-treatment LDL-C.[2] In AFCAPS/TexCAPS, although baseline LDL-C, HDL-C, and apo B were all significant predictors of risk for first major coronary events, only apo B remained significant in the analysis of on-treatment variables.[20] Recent post hoc analyses of pooled data from 18 018 subjects in the Treat to New Target (TNT) and Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) studies confirm these findings, with on-treatment levels of non-HDL-C and apo B more closely associated with CVD outcomes than LDL-C.[23] In addition to these observational findings and post hoc analyses, the randomized, double-blind Familial Atherosclerosis Treatment Study (FATS) was conducted in 162 men aged 52 years or younger with coronary artery disease and apo B levels 125 mg/dL or higher who were treated with conventional and intensive lipid-lowering therapy for 2.5 years.[24] Intensive lipid-lowering therapy (colestipol plus lovastatin or niacin) lowered LDL-C by 46% and 32%, respectively, while apo B fell from 159 to 103 mg/dL and from 155 to 111 mg/dL, respectively (both, $P<.001$ vs baseline). HDL-C increased by 15% and 43% with colestipol plus lovastatin and colestipol plus niacin, respectively. Intensive dyslipidemic therapy was associated with less frequent progression and more frequent regression of proximal arteries and a reduction in CVD events, compared with conventional therapy.[24] Regression of coronary lesions was best correlated with the percent change in apo B levels.[24]

Value of Apo A-I and the Apo B/Apo A-I Ratio as Risk Predictors

Evidence for apo A-I itself as a CVD risk predictor is relatively weak. A number of population-based studies have shown that apo A-I provided little or no additional predictive value compared with conventional parameters[25,26] and was not as strong a predictor as apo B.[14,19] Nonetheless, in the AMORIS study, low apo A-I was strongly and positively related to increased risk of MI, even in a model that included total cholesterol and triglycerides.[17] Other population-based data showed that apo A-I was more powerful than HDL-C in predicting CHD.[27]

Although the apo B/apo A-I ratio improved risk prediction only negligibly in 1 study[28] and was comparable to the total cholesterol/HDL-C ratio in another,[29] overall it appears that the predictive value of the apo B/apo A-I ratio is strong and possibly better than the use of either apolipoprotein alone. Among modifiable risk factors including smoking, diabetes, and hypertension that were evaluated in the large effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (INTERHEART) case-control study, an elevated apo B/apo A-I ratio had the strongest association with the risk of MI (odds ratio: 3.25 for top vs lowest quintile; population attributable risk, 49.2% for the top 4 quintiles vs the lowest quintiles).[30] In AFCAPS/TexCAPS, patients in the highest tertile of baseline apo B/apo A-I ratio had the highest risk for first major coronary events.[20] After 1 year of statin therapy, the predictive power of the apo B/apo A-I ratio remained, and slightly improved the risk prediction provided by apo B alone, whereas LDL-C and total cholesterol did not significantly predict risk either at baseline or after 1 year.[20] Moreover, in the TNT/IDEAL pooled analysis, the apo B/apo A-I ratio showed the strongest relationship with major CVD outcomes (hazard ratio: 1.24; 95% confidence interval: 1.20–1.29).[23] However, although the apo B/apo A-I ratio is a superior risk predictor compared with the single proatherogenic apo B level, clinical trial data demonstrating a beneficial effect of increasing apo A-I and HDL-C on CVD outcomes are lacking.

Role of Statins in Improving Apolipoprotein Profiles

The mechanism underlying the beneficial effects of statins on apolipoprotein metabolism is a subject of continuing investigation. Recent data in patients with metabolic syndrome suggest that statins decrease apo B by increasing catabolism of apo B-containing lipoproteins and, at higher doses, by decreasing LDL apo B production.[31] In hypertriglyceridemic patients, statins may decrease apo B by shifting the distribution of apo B from small, dense LDL particles to larger, more buoyant LDL particles.[32]

Levels of both apo B and apo A-I can be improved with statin therapy, as a number of clinical trials have shown that statins can lower apo B and the apo B/apo A-I ratio and, in some cases, increase apo A-I levels across broad populations of patients, including those with low HDL-C, metabolic syndrome, or type 2 diabetes.[33–36]

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Conclusions

Apo B and apo A-I are important markers of atherogenicity and atheroprotection, respectively. On the whole, data in healthy populations and in patients with specific lipid abnormalities and/or preexisting CVD support the concept that apo B is a better measure of CVD risk than LDL-C. Apo B may be particularly relevant in the setting of insulin-resistant states, such as diabetes and metabolic syndrome, as patients with these disorders often manifest normal LDL-C values, but have a preponderance of small, dense LDL particles and higher apo B. Incorporating apo B and the apo B/apo A-I ratio into risk assessment could therefore provide additional and important information on CVD risk. A recent Consensus Conference Report[12] recommended that apo B be added to risk assessment in persons at high cardiometabolic risk, with target levels of <90 mg/dL and <80 mg/dL in high risk and highest risk persons, respectively. Achieving this apo B goal will likely require intensive statin therapy, which has been shown to have beneficial effects on all apolipoproteins. Since apo B is not yet routinely measured in clinical practice, however, and since apo B is the primary apoprotein component of LDL-C, it is prudent at this time to continue to lower LDL-C levels aggressively using appropriate statin therapy. Although it provides superior risk discrimination, the apo B/apo A-I ratio cannot yet be recommended for routine clinical use, as clinical trial data showing the benefit on outcomes of increasing apo A-I and HDL-C are lacking.

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