Some practitioners use advanced lipoprotein analysis with the goal of better predicting risk and individualizing lifestyle and drug therapy for cardiovascular prevention. Unfortunately, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particle number and size, other lipoprotein subfractionation, apolipoproteins B and A, and lipoprotein(a) have not yet met current standards for biomarker evaluation, and it remains to be determined whether these tests incrementally add to cardiovascular risk predicted by traditional risk factors. More importantly, it has yet to be determined whether treatment strategies guided by, or targeting, these measures improve cardiovascular outcomes. Drug therapies known to alter advanced lipoprotein analysis parameters, specifically niacin and fenofibrate, have not been shown to additionally reduce cardiovascular risk in recent randomized trials of high-risk patients treated with statin therapy. These findings suggest advanced lipoprotein analysis–guided strategies may not further reduce cardiovascular events and could lead to increased adverse effects and costs; this approach needs further research to establish its role in individualizing therapies for cardiovascular prevention. In contrast, a large body of evidence supports focusing on LDL cholesterol reduction and intensification of statin therapy to reduce cardiovascular risk. (J Am Coll Cardiol 2012;60:2607–15) © 2012 by the American College of Cardiology Foundation

Clinicians continue searching for biomarkers that will facilitate the practice of personalized preventive medicine. Algorithms for predicting cardiovascular risk using traditional risk factors, such as the Framingham Risk Score recommended by the National Cholesterol Program Adult Treatment Panel III, provide an estimate of the probability that a patient will experience a coronary heart disease (CHD) event in the next 10 years. In contrast, the clinician would like an ideal biomarker, or biomarkers, that would give a definitive prediction (yes or no) of the individual patient’s risk of cardiovascular disease (CVD) to guide the intensity and type of therapy. For example, the Framingham Risk Score might estimate that a 45-year-old man with low-density lipoprotein cholesterol (LDL-C) of 125 mg/dl has a 5% risk of CHD in the next 10 years (1). The Adult Treatment Panel III recommendations would not consider him a candidate for lipid-modifying drug treatment (2). Additionally, he is too young (<50 years) and his C-reactive protein is too low (1.5 mg/dl) to meet the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) entry criteria (3). However, if an ideal biomarker could determine whether this person could be the 1 of 20 patients who go on to have a CHD event in the next 10 years, the clinician could then initiate more intensive lifestyle and/or drug therapy to reduce this patient’s cardiovascular risk. Conversely, if the biomarker were absent, the patient would then be among the 19 patients who do not experience a CHD event in the next 10 years, and drug treatment, and possibly more aggressive lifestyle changes, could be avoided.

Treatment guided by advanced lipoprotein analysis is 1 approach advocated by some to identify additional lipid and lipoprotein biomarkers to guide the initiation, type, and intensity of lipid-modifying therapy beyond the recommendations of the current guidelines (3–5). The rationale for this approach is that a substantial proportion of patients continue to have events, a concept promoted as “residual risk”. Some advanced lipoprotein analysis results have been incorporated into the most recent dyslipidemia guidelines, including apolipoprotein (apo) B, apo A-I, and lipoprotein(a) (Lp[a]) (6–8). This paper reviews whether there is sufficient evidence to support the use of advanced lipoprotein analysis as an ideal biomarker to better predict risk and to make personalized treatment decisions in individual patients, and future research directions are recommended (Table 1).

What Does Advanced Lipoprotein Analysis Measure?

Advanced lipoprotein analysis quantitates subpopulations of lipoproteins and apoproteins, including particle size and number,
particles are more atherogenic than large ones, but this relationship usually disappears in more fully adjusted analyses, including insulin resistance–associated factors, including diabetes, hypertriglyceridemia, low HDL-C, and apo B (12). Ratios of aps have also been proposed as better predictors of cardiovascular risk than conventional lipid levels or ratios (13). Lp(a) is a plasma protein composed of an LDL particle linked to apo(a), which has structural homology with plasminogen. Lp(a) may therefore contribute to both intimal cholesterol deposition and prothrombotic potential.

Advanced Lipoprotein Analysis Methods and Performance

No standardized laboratory methods for lipoprotein subclass distribution and quantitation have been established (12,14,15). The currently available commercial laboratory methods use a variety of methods to measure lipoprotein subfractions: gradient gel electrophoresis (Berkeley Heart Lab, Inc., Berkeley, California), nuclear magnetic resonance (NMR) (Liposcience, Inc, Raleigh, North Carolina), density gradient rapid ultracentrifugation (termed the “vertical auto profile” [VAP]; Atherotec, Birmingham, Alabama), and most recently, microfluidic gel electrophoresis using a chip technology (Quest Diagnostics Inc., Madison, New Jersey). Each method measures different physiochemical properties, such as size, charge, distribution of cholesterol, or magnetic resonance to estimate lipoprotein subclass distribution. An Agency for Healthcare Research and Quality–funded systematic review of reports published through June 2008 found widely varying agreement among methods (ranging from 7% to 94% concordance) for measuring LDL subfractions, such that measurements using different methods were not directly comparable (14).

In contrast, international standards exist for aps B and A-I. Apo B measurement with immunoassays (immunoturbidimetric, immunonephelometric, and radial immunodiffusion) have similar accuracy (16). However, VAP and NMR are the most commonly used methods for advance lipid testing, including apo B and A-I measurement, and have more variability. A 2011 study of >1,000 patients with combined hyperlipidemia and significant hypertriglyceridemia (those in whom measurement of conventional and advanced lipid measures are considered most discordant [17]) found that total apo B levels were highest using an immunonephelometric assay (Medical Research Laboratory International, Inc., Highland Heights, Kentucky), intermediate with NMR (14% lower than the immunonephelometric assay), and lowest with VAP (about 17% lower than the immunonephelometric assay) (18). Conversely, non-HDL-C levels were similar across the assays.

Measurement of Lp(a) has long been problematic due to interindividual variation in the number of kringle domains determining the length of the apo(a) moiety, which accounts for 90% of the plasma concentration of Lp(a) (19). Only recently have recommendations been made to standardize Lp(a) assays using apo(a) isoform insensitive assays that are

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<th>Agenda for Establishing the Role of Advanced Lipoprotein Analysis in Individualizing Treatment for Preventing Cardiovascular Disease</th>
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reproducible and inexpensive. A reference Lp(a) preparation was recently approved. However, there are large race-dependent variations in Lp(a) levels, and reference ranges for individual race/ethnicities have yet to be developed (19).

Modern standardized assays for plasma total cholesterol and HDL-C use standardized methods based on the current Centers for Disease Control and Prevention reference methods; these methods should result in a coefficient of variation of \(<4\%\) for calculated LDL-C (20). Small seasonal and long-term variations in LDL-C in statin-treated patients have been described (21,22). Whether similar changes occur in the components of advanced lipoprotein analysis have not yet been established.

Advanced Lipoprotein Analysis for Cardiovascular Disease Risk Prediction

Several recent systematic reviews and meta-analyses have evaluated the various components of advanced lipoprotein analysis for cardiovascular risk prediction. The previously noted Agency for Healthcare Research and Quality systematic review found each Lipoprotein subfractionation method used different criteria and definitions to classify the CHD risk of patients (14). No studies comparing the accuracy of various methods for predicting CVD risk were identified. The American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines more recently completed a systematic review of literature published between March 2008 and April 2010 (9). They found that the LDL particle number was found in many, but not all, studies to be independently associated with CVD outcomes after adjustment for established risk factors. Although LDL particle number predicted risk better than LDL-C, the risk predicted by LDL particle number was similar to that of more comprehensive measures of atherogenic particles, such as non–HDL-C or apo B.

Subsequent to these meta-analyses, an analysis of the MESA (Multi-Ethnic Study of Atherosclerosis) trial, which included 6,814 subjects free of CVD followed for 5.5 years, found that LDL-C and LDL particle number were associated with incident CVD in the overall cohort (23). However, only LDL particle number was associated with CVD risk in those whose LDL-C and LDL particle number differed by \(\geq 12\) percentage points (termed “discordant”). Not surprisingly, those who were discordant with the LDL particle number greater than LDL-C concentration had higher body mass index, waist circumference, measures of insulin resistance, and more frequently had metabolic syndrome and diabetes. No comparisons of LDL particle number to non–HDL-C or apo B were performed in this analysis. However, another analysis of MESA compared the ratio of total cholesterol/HDL-C with the ratio LDL particle number/HDL-C particle number (24). Both ratios were similarly excellent predictors of increased CVD risk, but the addition of the LDL particle number/HDL-C particle ratio did not meaningfully improve the C-statistic of the Framingham Risk Score based on total cholesterol and HDL-C levels. Nor did the LDL particle number/HDL-C particle ratio result in the net reclassification index of at-risk patients (0.1%).

Recent meta-analyses of apo B for CVD risk prediction had conflicting conclusions. The Emerging Risk Factors Collaboration performed an individual-level meta-analysis of 302,430 subjects free of vascular disease (25). Individual-level meta-analyses are generally considered more robust than study-level meta-analyses for a number of reasons, including many more data points and the ability to adjust for covariates at the individual level. In the 22 studies that measured both apolipoproteins and lipids, the apo B and the apo B/A-I ratio had very similar magnitudes of association as non–HDL-C and the total-C/HDL-C ratio after adjustment for other established risk factors.

A subsequent study-level meta-analysis by Sniderman et al. (26) included 15 studies and 233,455 subjects with and without CHD. Although the 95% confidence intervals (CIs) overlapped, the relative risk reduction in CVD events for lowering apo B were on average 6% higher than those for lowering non–HDL-C, and the relative risk reductions for lowering non–HDL-C were 5% higher than for lowering LDL-C. In contrast to the previous Emerging Risk Factors Collaboration individual-level analysis (25), no adjustment for other established risk factors was performed. However, in the small number of studies by population subgroup, there was no evidence that the relationship between apo B and non–HDL-C varied by diabetes status in the Sniderman et al. (26) trial-level analysis, one of the patient populations in whom apo B was considered by advocates to improve risk prediction.

The studies comparing advanced lipoprotein analysis-based risk prediction to conventional risk prediction methods (such as Framingham Risk Score), according to current standards for novel biomarker assessment, including discrimination, calibration, and reclassification (Table 1) (27), found no added risk prediction over conventional lipid measurements. In the previously described EPIC (European Prospective Investigations into Cancer and Nutrition)-Norfolk study, although the apo B/A-I ratio was independently associated with increased CHD risk, it did no better than conventional lipid values at discriminating between CHD cases and control subjects (area under the receiver-operating characteristic curve: 0.673 vs. 0.670, respectively; \(p = 0.38\)) (28). When the apo B/A-I ratio was added to the Framingham score, the area under the receiver-operating characteristic curve was slightly increased (0.613 vs. 0.594 without; \(p < 0.001\)). However, addition of the apo B/A-I ratio to the Framingham score resulted in incorrect classification of 41% of CVD cases and 50% of control subjects without CVD. Another analysis of the Framingham study had similar findings (29). Another analysis found that although lipoprotein particle, LDL, HDL, very low-density lipoprotein (VLDL) LDL/HDL concentration, and LDL, HDL, and VLDL particle size measured by NMR each
independently predicted risk after adjustment for nonlipid risk factors, these measures were not superior to total-C, LDL-C, HDL-C, apo B, apo A-I, or the apo B/A-I ratio (30). The addition of LDL particle size or apo B did not improve the C-index, nor did LDL particle size or apo B result in reclassification compared with a model that contained the total cholesterol, HDL-C, and nonlipid risk factors. Another analysis of a subgroup of women from the this study used an immunoturbidimetric method to measure apolipoprotein B and A-I and found that it had the same magnitude of risk prediction as non–HDL-C, both of which were superior to LDL-C (31). Moreover, HDL-C appeared to be a better risk predictor than apo A-I.

In summary, the various parameters of advanced lipoprotein analysis do not appear to improve CVD prediction over risk prediction strategies using conventional lipid measurements when evaluated according to current standards for biomarker evaluation.

Advanced Lipoprotein Analysis for Cardiovascular Disease Risk Prediction in Drug-Treated Patients

Based on an extensive body of evidence, statins are the evidence-based treatment of choice, with statin treatment initiation based on LDL-C and risk level (1,2,32). Therefore, a more clinically applicable use of advanced lipoprotein analysis is for risk prediction in statin-treated patients to guide further intensification of lipid therapy. To examine this concept in patients with CHD receiving statin therapy, an analysis pooling the TNT (Treating to New Targets) and IDEAL (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering) study populations found that on-treatment levels of non–HDL-C and apo B were better predictors of CVD risk reduction from statin treatment than on-treatment LDL-C levels (33). In addition, in those with LDL-C ≤100 mg/dl on statin therapy, non–HDL-C and apo B similarly predicted CVD risk. Furthermore, in those with non–HDL-C ≤130 mg/dl or apo B ≤110 mg/dl, non–HDL-C and apo B levels had almost identical risk prediction performance. Another analysis from the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22) trial also found that on-treatment non–HDL-C provided additional risk prediction over on-treatment LDL-C levels, but the on-treatment apo B/AI ratio did not (34).

Two analyses evaluated primary prevention statin trials. In the AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) trial, on-treatment percent changes in LDL-C, HDL-C, and apo B did not predict CHD risk reduction, although percent change in apo A1 and apo B/A-I did (35). Comparing on-treatment levels, the achieved apo B and apo B/A-I ratio predicted CHD risk reduction better than achieved LDL-C level, but no comparison was made to on-treatment non–HDL-C level. In JUPITER, those on rosuvastatin 20 mg who had an on-treatment C-reactive protein <2 mg/l were at lower risk regardless of apo B above or below 80 mg/dl (36); conversely, in those with C-reactive protein ≥2 mg/l, those with apo B ≥80 mg/dl were at higher risk than those with apo B <80 mg/dl.

A recent individual-level meta-analysis pooled data from 8 primary and secondary prevention statin trials, including the 4S (Simvastatin Survival Study), AFCAPS, LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease), CARDS (Collaborative Atorvastatin Diabetes Study), TNT, IDEAL, SPARCL (Stroke Prevention by Aggressive Reduction of Cholesterol Levels), and JUPITER (n = 38,153) trials (37). Changes in non–HDL-C and apo B in statin-treated patients similarly predicted reduction in CVD risk slightly better than LDL-C. Changes in non–HDL-C and apo B similarly predicted CVD reduction in all subpopulations studied, including those with diabetes and triglycerides ≥150 or <150 mg/dl. Interestingly, the proportion of the treatment effect explained by the reduction in non–HDL-C (64%) was greater than that explained by the reduction in apo B (54%; p = 0.007) or LDL-C (50%; p < 0.001).

In summary, all patients requiring cholesterol-lowering drug therapy for CVD risk reduction should receive a statin as first-line therapy. Change in non–HDL-C appears to be superior to apo B or LDL-C changes for predicting the magnitude of CVD reduction in statin-treated patients.

Treatment Outcomes

Regardless of whether advanced lipoprotein analysis improves cardiovascular risk prediction (although there is evidence that it may not, as reviewed previously), the most important question is whether therapeutic strategies guided by advanced lipoprotein analysis improve outcomes compared with fixed-dose therapy or compared with strategies titrating to LDL-C and/or non–HDL-C goals. Unfortunately, no clinical trials have yet been performed to answer this question. However, observational evidence is available from randomized trials. Although the SANDS (Stop Atherosclerosis in Native Diabetics Study), ACCORD (Action to Control Cardiovascular Risk in Diabetes), and AIM-HIGH (The Ateroatherosclerosis Intervention in Metabolic syndrome with low HDL/high triglycerides) trials did not use advanced lipoprotein analysis to direct treatment, these trials evaluated whether combining a statin with a second lipid-modifying agent with significant effects on advanced lipoprotein analysis parameters would improve cardiovascular outcomes compared with statin monotherapy. A careful evaluation of these trials may yield helpful information for determining the role of advanced lipoprotein analysis for guiding the intensity of therapy.

SANDS. SANDS randomized participants with type 2 diabetes to either aggressive treatment (LDL-C ≤70 mg/dl, non–HDL-C ≤100 mg/dl, and systolic blood pressure ≤115 mm Hg) or standard treatment (LDL-C ≤100
mg/dl, non–HDL-C ≤130 mg/dl, and systolic blood pressure ≤130 mm Hg) targets (38). The treatment algorithm started with lifestyle modification, then added a statin if needed; if the LDL-C goal was not achieved on a statin, ezetimibe was added; if the non–HDL-C goal was not achieved on a statin, fish oil, fenofibrate, or niacin were added. After 3 years of treatment in SANDS, carotid intima media thickness (CIMT) regressed in the aggressive treatment group and progressed in the standard treatment group. LDL-C, non–HDL-C, triglycerides, and apo B were significantly reduced in the aggressive treatment group compared with the standard treatment group, as were total, medium, and small VLDL particles; VLDL size; total, small, and large HDL particles; and apo B (39). There were no differences in HDL-C; large VLDL particles; LDL size; total, large, and small HDL-C; or HDL size between the 2 groups. Decreases in both LDL-C (p = 0.005) and non–HDL-C (p = 0.012) were correlated with CIMT regression. Apo B had similar associations as non–HDL-C across quartiles, but did not quite achieve statistical significance (p = 0.07). In contrast, reduction in LDL particles had no consistent relationship with CIMT regression and was not significant (p = 0.09). It should be noted that greater CIMT regression was seen in those in the aggressive group who achieved an LDL-C ≤73 mg/dl.

ACCORD. The ACCORD trial compared more intensive treatment with standard treatment for diabetes control, lipids, and blood pressure in patients with type 2 diabetes (40). In the ACCORD lipid trial, all participants received background open-label simvastatin and were randomized to fenofibrate or placebo, with a 4.7-year follow-up (41). At baseline, LDL-C levels were 101 mg/dl, and by the end of the trial, mean LDL-C levels were very similar in both treatment arms (81 vs. 80 mg/dl, respectively). At baseline, median glycosylated hemoglobin levels were 8.1%, and were reduced to 7.5% in the standard therapy and to 6.4% in the intensive glycemic control groups. All major lipid parameters continued to improve in both treatment arms during the trial, possibly as a result of better glycemic control. By trial end, mean HDL-C levels increased from 38.0 to 41.2 mg/dl in the fenofibrate group and from 38.2 to 40.4 mg/dl in the placebo group; median triglyceride levels decreased from 164 to 122 mg/dl in the fenofibrate group and from 160 to 144 mg/dl in the placebo group. No differences in the primary cardiovascular outcome (hazard ratio: 0.92; 95% CI: 0.79 to 1.08; p = 0.32) or any secondary outcome were found. In prespecified subgroup analyses, there was a suggestion of harm in women, but a benefit in men (interaction p = 0.01) and a suggestion of benefit in those with both HDL-C ≤34 mg/dl and triglycerides ≥204 mg/dl (but no benefit in those without; interaction p = 0.057). The low HDL-C/high triglyceride subgroup comprised only 17% of the study population with well-controlled type 2 diabetes.

Advanced lipoprotein analyses have not yet been performed in the ACCORD trial. Therefore, a systematic review was undertaken using PubMed to identify fenofibrate–statin efficacy trials measuring particle size, number, apoprotein, or Lp(a). A 12-week efficacy trial in 300 dyslipidemic diabetic participants had baseline and on-treatment lipid levels fairly similar to those in the ACCORD trial and evaluated changes in particle number and size (VAP II) (42,43). The on-treatment levels on simvastatin 20 mg in this trial (LDL-C 92 mg/dl, HDL-C 39 mg/dl, triglycerides 183 mg/dl, and non–HDL-C 130 mg/dl) were fairly similar to those observed at baseline in the ACCORD trial, where 65% of patients were on a lipid medication at baseline (60% on a statin) and were not washed out. In comparison to the ACCORD trial, baseline lipids were LDL-C 101 mg/dl, HDL-C 38 mg/dl, triglycerides 160 to 164 mg/dl, and non–HDL-C 137 mg/dl (41).

Fenofibrate 160 mg added to simvastatin 20 mg further reduced LDL pattern B (LDL₃ + LDL₄) 4 mg/dl (~6%), increased buoyant LDL (LDL₁ + LDL₂, also known as pattern A) by 14 mg/dl (33%), increased LDL₄ by 3.4 mg/dl (11%), increased dense VLDL 3.9 mg/dl (16%), and increased intermediate-density lipoprotein 2.5 mg/dl (10%). Neither treatment had an effect on Lp(a).

Contrasting the effect of fenofibrate–statin combination with high-intensity statin therapy, an analysis comparing lipoprotein subclasses (VAP II), apo B, and conventional lipid markers found that both atorvastatin 80 mg and the combination drugs ezetimibe 10 mg + atorvastatin 40 mg reduced LDL-C, the cholesterol content of most LDL subfractions (LDL₁₋₄), apo B, and non–HDL-C (44,45). However, these treatments did not reduce the proportion of smaller, more dense, LDL particles. The proportion of pattern B increased in patients with triglycerides <150 and ≥150 mg/dl. Note that atorvastatin 80 mg was shown to reduce CVD events in 3 clinical trials that enrolled >20,000 subjects (46–48). Therefore, use of alternate therapy, such as the simvastatin plus fenofibrate used in the ACCORD trial, based on pattern B information might lead to the use of less efficacious therapy than atorvastatin 80 mg or other intensive LDL-C lowering agents in many patients.

The ACCORD trial found that the majority of diabetic patients with LDL-C levels <100 mg/dl (the mean in the ACCORD trial was about 80 mg/dl in both treatment groups) and reasonably well-controlled diabetes and blood pressure were unlikely to experience any benefit from the addition of fenofibrate to a moderate-dose statin. The projected changes in particle size and number from the addition of fenofibrate were unlikely to have contributed any additional risk reduction to the LDL-C lowering from simvastatin therapy. It has yet to be determined whether the very small subgroup of patients in the ACCORD trial with low LDL-C along with high triglycerides would benefit more from intensive statin therapy than they did from lower dose statin therapy combined with fenofibrate. The mean dose of simvastatin in the ACCORD trial was 22 mg/dl in both the fenofibrate and placebo groups. As previously noted, both the TNT and IDEAL trials found atorvastatin 80 mg
reduced CVD events more than moderate intensity statin therapy (simvastatin 20 to 40 mg or atorvastatin 10 mg) and, in contrast to the ACCORD trial, these trials found a substantial significant reduction in CVD events in the atorvastatin 80 mg group, regardless of baseline HDL-C or triglyceride levels (46,48).

In terms of non-cardiovascular outcomes, fenofibrate was shown to reduce the risk of retinopathy progression (although it did increase creatinine) in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial, but no such data were available for atorvastatin (49). Therefore, in the absence of a trial comparing statin–fenofibrate therapy to intensive statin therapy (such as atorvastatin 80 mg or another statin that lowers LDL-C by approximately 50%), or trials titrating therapy to advanced lipoprotein testing parameters, intensive statin therapy should remain the treatment of choice in dyslipidemic patients and in those with diabetes.

**AIM-HIGH.** The purpose of the AIM-HIGH trial was to determine whether adding niacin to simvastatin was superior to simvastatin alone for reducing cardiovascular risk in dyslipidemic patients with CVD who had similar on-treatment LDL-C levels (50). The AIM-HIGH trial randomized 3,414 participants to extended-release (ER) niacin 1,500 to 2,000 mg/day or a matching placebo (with 50 to 100 mg of immediate-release niacin to maintain the blind). Both groups received simvastatin 40 mg at baseline, the dose of which could be adjusted, or ezetimibe was added, to achieve an LDL-C of 40 to 80 mg/dl. Simvastatin 40 mg was received by 50% of participants in both groups (simvastatin 80 mg by 28% of the placebo group and 18% of the ER niacin group). Ezetimibe 10 mg was received by 21.5% of the placebo group and 9.5% of the ER niacin group. At 1 year, the mean LDL-C was 66 ± 20 mg/dl in the ER niacin group and 70 ± 19 mg/dl in the placebo group. When the change from baseline was compared between the 2 groups, the niacin group had 14% higher HDL-C, 23% lower triglycerides, 16% lower non–HDL-C, 10% lower apo B, 5% higher apo A, 19% lower Lp(a), 50% higher HDL2, and 10% higher HDL3.

The AIM-HIGH trial was terminated early with a median 3 years of follow-up due to futility, as well as a nonsignificant excess of strokes in the niacin group. Although the trial was criticized for its relatively small sample size, the survival curves were directly superimposable: a longer trial would have been highly unlikely to reveal a separation of the survival curves, and hence was terminated. Therefore, it could reasonably be concluded from the AIM-HIGH trial that niacin-induced changes in non-LDL-C lipid parameters (including, it should be noted, non–HDL-C). In patients with well-controlled LDL-C, niacin appeared to provide no additional cardiovascular risk reduction benefit. A strategy of simvastatin plus ER niacin 1,500 to 2,000 mg (with or without ezetimibe) appeared equivalent to simvastatin (with or without ezetimibe), which achieved on-treatment LDL-C of 40 to 80 mg/dl. AIM-HIGH therefore suggests that use of niacin to target various lipid fractions other than LDL-C might provide no particular advantage and might increase adverse effects (significant cutaneous adverse effects as well as less commonly serious muscle symptoms, gout, atrial fibrillation, type 2 diabetes, and gastric ulcers) and costs (discussed in the next section) (50,51). In addition, in the AIM-HIGH trial, a nonsignificant excess of strokes was observed in the ER niacin group (30 vs. 18 in the placebo group; hazard ratio: 1.67; 95% CI: 0.93 to 2.99; p = 0.09) (50). The importance of this finding was unclear, because 8 of the strokes in the niacin group occurred after niacin was discontinued between 2 months and 4 years. No excess of stroke was observed in the Coronary Drug Project, a trial comparing approximately 2 g immediate-release niacin with placebo in men with CHD and hypercholesterolemia (52).

It was argued that HDL-C levels did not differ enough between the ER niacin–simvastatin and placebo-simvastatin groups. However, on the basis of previous epidemiological studies where each 1 mg/dl increment in HDL-C was associated with a 2% to 3% reduction in CHD risk (53), it was expected to see at least some difference (albeit perhaps not significant) in the survival curves if the 5.2 mg/dl HDL-C in the ER niacin group reduced CVD risk by 10% to 16%. After examining the AIM-HIGH trial results, it is more difficult to support the argument of advocates of advanced lipoprotein analysis to intensify treatment to improve all abnormal parameters, because this argument assumes that such improvements would be additive to the increase in HDL-C. It should also be noted that apo B was <80 mg/dl in both the ER niacin group and placebo groups of the AIM-HIGH trial. An apo B <80 mg/dl was identified as the third target of therapy, after LDL-C and non–HDL-C, for the highest risk patients in a joint statement from the American Diabetes Association and American College of Cardiology (6).

Another observation is that in both the ACCORD and AIM-HIGH trials, the majority of participants were on statin therapy at baseline (60% and 93%, respectively) (48). In the AIM-HIGH trial, 76% were on a statin >1 year. Long-term statin therapy has been shown to stabilize plaque, and it might be difficult to demonstrate additional benefit from incremental lipid changes in these patients. For example, after the 2 years of simvastatin 40 mg therapy in the ASAP (Atorvastatin versus Simvastatin on Atherosclerosis) trial, no further reduction in CIMT was observed after 2 more years of follow-up when the simvastatin 40 group was switched to atorvastatin 80 mg (54).

**Cost Effectiveness**

A cost-effectiveness analysis of the SANDS trial found the more aggressive treatment group had slightly lower medical costs than the standard group, but 54% greater costs for antihypertensive medications ($1,242) and 116% greater costs for lipid-lowering medications ($2,863) over 3 years.
Those in the aggressive group gained 0.05 quality-adjusted life-years (QALYs) over the standard group. However, at a 3% discount rate, a cost per QALY of $82,589 would not be considered cost effective. Alternate scenarios reducing the cost of medications by 25%, 50%, and 75% resulted in cost per QALY of $61,329, $40,070, and $18,810, respectively, suggesting that exclusive use of lower cost generic medications could make aggressive treatment of LDL-C, non–HDL-C, and blood pressure a cost-effective option at a threshold of <$50,000 per QALY. It is unlikely that even more aggressive therapy targeting additional lipoprotein parameters (e.g., apo B was proposed [7]), if it requires additional full-cost patent-protected drugs, will be cost effective unless large reductions in cardiovascular events occur.

Conclusions and Research Recommendations

Proponents of advanced lipoprotein analysis argue that: 1) these tests lend further insight into important disturbances in lipid metabolism that explain the failure of LDL-C lowering strategies to eliminate cardiovascular events; and 2) therapies directed toward correcting the residual risk due to these abnormalities will further reduce cardiovascular risk. Unfortunately, these 2 hypotheses may be fundamentally flawed for a number of reasons. First, many of the lipoprotein and apo abnormalities detected with advanced lipoprotein analysis are the result of insulin resistance, and the excess cardiovascular risk associated with many of the advanced lipoprotein analysis abnormalities in epidemiological studies largely disappears after more complete adjustment for insulin resistance-related characteristics, including adiposity, hyperglycemia, hypertension, hypertriglyceridemia, and low HDL-C, and physical inactivity. These insulin-resistance characteristics are already assessed by the clinician in routine practice. Lifestyle intervention is the most appropriate strategy for reducing residual risk due to insulin resistance; several diabetes prevention trials demonstrated marked reductions in progression to diabetes with moderate weight loss and increasing moderate aerobic physical activity (56). It is not clear how intensification of drug therapies directed specifically at correcting lipid abnormalities would improve an insulin resistant state. Second, it is not clear how correcting lipid abnormalities would address the residual risk of other well-established cardiovascular risk factors, such as aging, male sex, hypertension, or smoking.

Third, it is not clear that advanced lipoprotein testing adds much information to what is already known from a fasting lipid panel, despite significant additional cost (57). Non–HDL-C is calculated from total cholesterol minus HDL-C at no additional charge, and appears to capture the information provided by advanced lipoprotein analysis measures.

Fourth, it seems naïve to believe that patients with residual risk due to an advanced burden of atherosclerosis will be “cured” with the 5 or so years of LDL-C lowering that occurred in the statin trials. Most of those arguing for residual risk in statin trials quote only a 30% reduction in cardiovascular events in the statin trials. Although this is accurate for moderately intensive statin therapy, more intensive statin therapy that lowers LDL-C by 50% (such as atorvastatin 80 mg or rosvastatin 20 mg) has been shown to reduce cardiovascular risk by about 45% compared with placebo, even when baseline LDL-C levels are <130 mg/dl (3,46–48). Meta-analysis of the statin trials found the reduction in cardiovascular events to be directly related to the magnitude of LDL-C lowering, with every 39 mg/dl (1 mmol/l) resulting in an additional 22% reduction in cardiovascular events across a wide range of baseline LDL-C levels (32). Therefore, intensification of statin therapy should be used as the first-line approach for more aggressive lipid management. If a patient has lipid abnormalities on a more intensive statin, the benefits, harms, and benefit–cost ratio of additional of second or third agents has yet to be established. Also of concern is how the additional agents, or more intensive LDL-C lowering, will influence the very modest increased risk of incident diabetes observed with statin therapy (about 1 to 3 additional diabetes cases per 1,000 patients treated per year) (3,58).

Fifth, although assessment of advanced lipoprotein analysis parameters such as apo B, LDL particle number, and Lp(a) have been advocated by some as reasonable for many intermediate- and high-risk patients (59), to date, clinical trial data do not support the superiority of treatment strategies incorporating nonstatin lipid-modifying agents compared with intensive statin therapy. The AIM-HIGH trial found that niacin-induced non–LDL-C lipoprotein and apo changes were not associated with further improvement in outcomes when LDL-C was lowered to 40 to 80 mg/dl, nor did ACCORD find overall benefit from adding fenofibrate to a lower dose of simvastatin in a dyslipidemic population of diabetic patients with mean LDL-C levels of 80 mg/dl, despite what were likely substantial changes in LDL-C particle size distribution and VLDL levels. A surrogate endpoint trial found reductions in non–HDL-C, and apo B predicted improvements in CIMT, but the LDL particle number did not; moreover, the aggressive statin-based treatment strategy used in this trial was only cost effective if generic medications were used (38).

In summary, in the current evidence-based practice environment, there is insufficient evidence to support the use of advanced lipoprotein analysis in clinical practice. Basic requirements for diagnostic and prognostic testing in clinical practice have yet to be met by many of the parameters measured in advanced lipoprotein analysis, nor has advanced lipoprotein analysis met the most important criteria needed to incorporate a new biomarker, technology, or treatment into clinical practice, which is, “Does this additional information improve clinical outcomes?” In the absence of evidence of improved clinical outcomes, benefit–cost analysis cannot be performed.
Table 1 outlines a research agenda for establishing the role of advanced lipoprotein analysis in individualizing therapy to prevent CVD. Outcomes from trials evaluating strategies based on advanced lipoprotein analysis will also need to include adverse effects, quality of life, and benefit-cost analyses, especially as the population at risk for CVD becomes increasingly diverse and advanced in age.

Reprints and correspondence: Dr. Jennifer G. Robinson, Department of Epidemiology & Medicine, University of Iowa, 105 River Street, Iowa City, Iowa 52242. E-mail: jennifer-g-robinson@uiowa.edu.

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