

Foreword



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This issue, written by experts in the field of lipidology and compiled by Donald Smith, brings to the reader both basic aspects and clinical applicability.

An important question that often arises is the benefit of ordering more advanced lipoprotein profiles. The main reason for the quandary, as pointed out in the article by Lau and Smith, is that calculated low-density lipoprotein (LDL) cholesterol, measured by standard technologies, or non-high-density lipoprotein (non-HDL) cholesterol, are less predictive of ischemic cardiovascular risk than are apolipoprotein B (apoB) and nuclear magnetic resonance (NMR)-measured LDL particles in numerous studies. This is especially true in the presence of high triglycerides, or low-HDL cholesterol. Although apoB levels and the number of NMR-measured LDL particles may be more predictive, no clinical trials comparing the use of these goals versus LDL cholesterol or non-HDL cholesterol goals have been performed. For those who can interpret the results, their use may be justified occasionally to confirm lipid goal attainment in those with mixed dyslipidemias and particularly in patients already at standard lipid goals in the presence of progressive coronary heart disease.

Prediction of coronary heart disease is extremely important in clinical practice for primary and secondary prevention. Wilson emphasizes in his article the importance of standardizing baseline measurements of the factors involved, such as the lipid profile and diabetes status, to enable outcome studies to lead to definitive decisions. It has been established that the Framingham score is still very useful as a predictive index except in Japanese-Americans and in African Americans. In addition, investigators in certain European countries have found that, while Framingham is useful, it may overestimate cardiovascular disease in some groups, such as Italians. Future estimates will undoubtedly add other biomarkers and imaging techniques for atheromatous burden, and eventually may add genetic markers to aid in the predictions.

An important aspect of lipid management involves lifestyle changes. Katcher, Hill, Lanford, Yoo, and Kris-Etherton comprehensively discuss dietary components contributing to elevated LDL cholesterol, including saturated fat, trans fats, and cholesterol. They present descriptions and clinical trial evidence of various dietary manipulations that can significantly alter the lipoprotein profile, including weight reduction and diets that include more soluble fiber, plant sterols, and soy, all having variable

quantitative effects. In a separate section, the effects of low-carbohydrate and Mediterranean diets, omega 3 fatty acids, mono-unsaturated fatty acids, and alcohol on triglycerides and HDL cholesterol are presented. Finally the lipid-altering effects of physical exercise are discussed as an important component of lifestyle change that should always complement these dietary manipulations.

The minimal goal for reductions in LDL cholesterol is 40 mg/dL (1 mM/L). This is often achieved by a single statin drug, though often the practitioner has to consider additional therapies. Hou and Goldberg discuss these options and describe the mechanisms of action and practical aspects of their usage. The major drugs discussed are statins, ezetimibe, and bile acid sequestrants, as well as niacin and fibrates. Combination therapies have indeed reduced LDL cholesterol levels further and studies are ongoing to quantify their preventive effects in the clinical environment.

Research progresses on other new medications and other methodologies to reduce LDL cholesterol. Evan Stein has been involved in many of these early-phase clinical trials. He describes in detail compounds being studied that not only provide possible new therapies, but also illustrate the biochemistry of lipid metabolism and the safety problems of interfering with it. Compounds discussed include squalene synthase inhibitors, apoB antisense oligonucleotides, small interfering RNAs of apoB, and proprotein convertase subtilisin kexin 9.

Venero and Thompson in their article describe the etiology and management of statin-induced myopathy, an important clinical problem given the widespread use of statins. The incidence as reported in clinical trials of approximately 5% is lower than that found in surveys of patients in clinical practice, where incidence is around 10%. The symptoms range from tolerable myalgias to fatal rhabdomyolysis in extremely rare cases. Creatine kinase measurements may be important at baseline with repeat testing only necessary when the patient actually experiences myopathic symptoms. Stopping the agent, reintroducing a different statin, increasing the dosing interval, and even trying coenzyme Q10 are suggested therapeutic ways to handle this.

Ira Goldberg discusses the value of treating hypertriglyceridemia. While treatment of hypercholesterolemia with statins and other agents has shown clear-cut results in preventing cardiovascular events, and while the treatment of very elevated triglycerides to prevent pancreatitis is important, the value of treating moderate hypertriglyceridemia to prevent such cardiovascular events is debatable. There are numerous dietary regimens and drugs that can effectively lower triglycerides and they are effective both for very high levels (>500 mg/dL) as well as for levels below 500 mg/dL. Despite inconsistent evidence in preventive clinical trials, lowering triglycerides to below 150 mg/dL in patients at risk is considered a secondary lipid-altering goal, which often also provides the additional benefit of raising HDL cholesterol.

An important risk factor for the development of atheromatous cardiovascular disease is reduced HDL cholesterol, and a few trials have shown that raising HDL cholesterol reduces cardiovascular risk. While statins are extremely effective in reducing LDL cholesterol, they are only mildly effective in raising HDL cholesterol. Drugs, such as niacin, and fibrates in the presence of hypertriglyceridemia are more effective. Peter Toth describes efforts to find agents that will raise HDL cholesterol. Investigators have looked into therapies involving apolipoprotein A1 (apoA1) itself, apoA1-mimetics, novel peroxisome proliferator-activated receptor alpha agonists, liver X receptor alpha agonists, cholesterol ester transfer protein inhibitors, and farnesoid X receptor antagonists. To date these agents, while demonstrating effectiveness in preclinical studies and in some clinical studies, are not yet adequately developed for use in patients.

Atherosclerosis can clearly begin in childhood and adolescence. Initially it was thought to be purely the consequence of genetic causes, such as familial hypercholesterolemia. However, with the epidemic of obesity that is affecting youth, environmental factors normally involved in atherosclerosis in adults are clearly in play. Dietary intervention and lifestyle changes are clearly indicated to reverse these processes. On the other hand, in cases of familial hyperlipidemia and in those adolescents that fail lifestyle intervention and are at high risk, pharmacological intervention is clearly indicated. Zappalla and Gidding develop these issues in their article.

Nair and Darrow address the important topic of lipid management in the geriatric patient. As the population ages, more patients are at risk for cardiovascular disease. Such patients require lipid-lowering agents for primary and secondary prevention, a strategy that has been shown to work quite effectively in a number of well-known trials. Statins are particularly useful. However, when statins are inadequate as solo agents, combinations with other lipid-altering therapies should be considered, as in the nongeriatric age group. Judicious usage is essential, especially when considering high doses, as the elderly are more prone to the known side effects. However, this caution should not result in avoidance of prescribing these agents to the elderly with dyslipidemia.

Use of anti-retroviral agents in treating HIV-infected individuals commonly results in dyslipidemia. Once dyslipidemia appears, there are two therapeutic approaches: altering the anti-retroviral therapy or initiating therapy for the dyslipidemia. These therapies, however, may interfere with each other, as outlined in the article by Judith Aberg. If changes in anti-retrovirals is undertaken to affect the lipid profile, it should be done under supervision to maintain virologic suppression. Nutritional alternatives to lipid therapy should undoubtedly be considered first.

Chronic kidney disease is associated with increased cardiovascular morbidity and mortality. Montague and Murphy discuss the notion that, while numerous factors may account for this effect, the role of lipid abnormalities is unclear. This arises from two important aspects. One is the fact that, in end-stage renal disease with patients on dialysis, the profile of lipid abnormalities changes from that seen in the general population. Total cholesterol, LDL cholesterol, and HDL cholesterol may all be lower, whereas small dense LDL particles and lipoprotein (a) may increase. Furthermore, only a few clinical trials using lipid-lowering drugs have been completed, while others are ongoing. All in all, the clinical-trial preventive evidence is not yet clear-cut.

I believe that this up-to-date presentation will be of tremendous value and will be most appreciated by all of us involved in an important area of endocrinology.

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