abstract

Substantial data from epidemiologic, lipid intervention and serial coronary angiographic studies have established the importance of high-density lipoprotein cholesterol (HDL-C) on cardiovascular risk. Low levels of HDL-C should be treated with non-pharmacologic therapy, including weight reduction and aerobic exercise training. Persistently low levels of HDL-C can be treated with niacin therapy, fibrates (especially if the triglyceride levels are elevated) and the statin family of medications. For every 1% increase in HDL-C, one would expect a greater than 3% reduction in vascular risk.

Key words: high-density lipoprotein, niacin, fibrates, statins, exercise.

Importance and Management of Low Levels of High-density Lipoprotein Cholesterol in Older Adults

Part II: Screening and Treatment

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In the previous (March) issue, we reviewed the role and mechanism of high-density lipoprotein cholesterol in older adults. Here, we review recommendations for the screening and treatment of low levels of HDL-C in older adults.

Introduction

Low high-density lipoprotein cholesterol (HDL-C) levels have been identified clearly as a major, independent risk factor for coronary artery disease (CAD), based on epidemiologic, lipid intervention and coronary angiographic studies.[1,2] HDL-C operates as a continuous variable,[3] with a stronger relationship to CAD than high total cholesterol or low-density lipoprotein cholesterol (LDL-C) levels. Moreover, in some studies it has been found to be more prevalent in cases of CAD than high LDL-C levels.[4] Additionally, HDL-C not only provides significant, independent prognostic information, but it is also a reliable marker for the atherogenic LDL-C fraction.

Therefore, it is very important to routinely screen patients for this risk factor as part of the risk assessment and management of CAD, irrespective of the patients's age. Without the routine measurement of HDL-C, a significant number of high-risk patients would not be identified for any beneficial lipid intervention or treatment. Additionally, the therapeutic goal for LDL-C would not be appropriately established because of sub-estimation of CAD risk. Patients with concomitantly elevated LDL-C and low HDL-C, especially in the presence of hypertriglyceridemia (lipid triad), have a higher incidence of CAD events and receive a greater benefit from statin therapy than patients with elevated LDL-C and normal or elevated HDL-C.[5]

Although all of these concepts also apply to the older population, there are a few caveats that need special attention. The decision to treat an older patient for low HDL-C (as well as high LDL-C) should be made after considering the net benefit to be gained if other life-limiting comorbidities exist, which may affect the long-term treatment of various lipid abnormalities. Toxicity and drug interactions may be a limiting step in the use of medications. However, there is positive evidence from several studies for the use of both non-pharmacologic and pharmacologic treatments in older patients with low HDL-C.[6,7,8] Even though there is less data on primary prevention (although the majority of patients in PROSPER represented primary prevention or "soft" prior CAD, such as angina pectoris[6]), the large absolute number of older patients developing overt CAD and its related complications supports the need to intervene in these patients.

The NCEP/ATP III guidelines established an HDL-C level < 40mg/dL as low and > 60mg/dL as high. Due to absence of substantial data, treatment of low HDL-C is generally considered when other risk factors are present or it is considered a secondary target after treating LDL-C (Third Report). We

believe, however, that the current guidelines still do not satisfactorily emphasize the importance of low HDL-C treatment. More stringent guidelines regarding assessment and management of low HDL-C also have been published.[9]

Non-pharmacologic Management of Low HDL-C

Since low levels of HDL-C frequently coexist with hypertriglyceridemia, treatment of these patients is usually directed toward reduction of triglyceride levels, frequently leading to significant increases in HDL-C. Similarly, when non-HDL cholesterol levels and/or LDL-C levels are elevated, such lipid abnormalities should be treated first, before considering the initiation of pharmacologic therapy to raise HDL-C.

The management of isolated low HDL-C in primary prevention consists mainly of non-pharmacologic measures (Table 1). However, drug treatment needs to be considered in high-risk patients who demonstrate persistently low HDL-C levels in spite of aggressive non-pharmacologic therapy.

Due to the strong association between low HDL-C and atherogenic dyslipidemia and emerging risk factors, patients with isolated low HDL-C could be evaluated for subclinical (occult) atherosclerotic vascular disease. Those patients can be screened with treadmill testing, non-invasive carotid testing or coronary calcium screening, and their level of inflammation also can be assessed with measurement of high-sensitivity C-reactive protein. This practice will help identify the higher risk population that may be more likely to benefit from pharmacologic therapy aimed at both increasing HDL-C and reducing LDL-C, especially when non-pharmacologic treatment fails to significantly alter HDL-C.

Diet

No specific diet other than caloric restriction with resulting weight loss has been shown to raise HDL-C. However, diets low in saturated fat and cholesterol decrease both LDL-C and HDL-C. The lowering of HDL-C that often occurs with a diet restricted in saturated fat can be limited/compensated by exercise and weight reduction.[10] Diets high in monounsaturated fats generally maintain HDL-C while lowering LDL-C levels, whereas diets with very high carbohydrate content (> 60% of total calories) are accompanied by a reduction in HDL-C and a rise in triglycerides, and should therefore be avoided.[4,11] We recommend a Mediterranean-type diet that is low in saturated fat, but relatively high in monounsaturated fats and fish oils. It allows improvement of the overall lipid profile, maintenance of HDL-C levels and prevention of CAD and cancer.[12] In summary, we believe that restriction of total fat and calories, the consumption of modest amounts of monounsaturated fats (including olive, peanut and canola oils) in place of saturated fats, the use of liquid margarines (when necessary) and increased consumption of fatty fish comprise a safe and prudent diet for patients with low HDL-C.[4]

Table 1: Non-parmacological Management of Low High-density Lipoprotein Cholesterol[4]

Increased physical activity
Weight loss
Reduction of cholesterol-raising foods
Smoking cessation
Moderate alcohol consumption
Discontinuation of HDL-lowering medications

Table 2: Pharmacological Management of Low High-density Lipoprotein Cholesterol

Agent	Percentage increase of HDL-C[a]
Nicotinic acid	20–40%
Gemfibrozil	5–20%
Fenofibrate	10–25%
Statins[b]	0–15%

[a]See text for percentage increase of HDL-C with different combinations of agents.
[b]See text for possible differences between statins at various dosages.

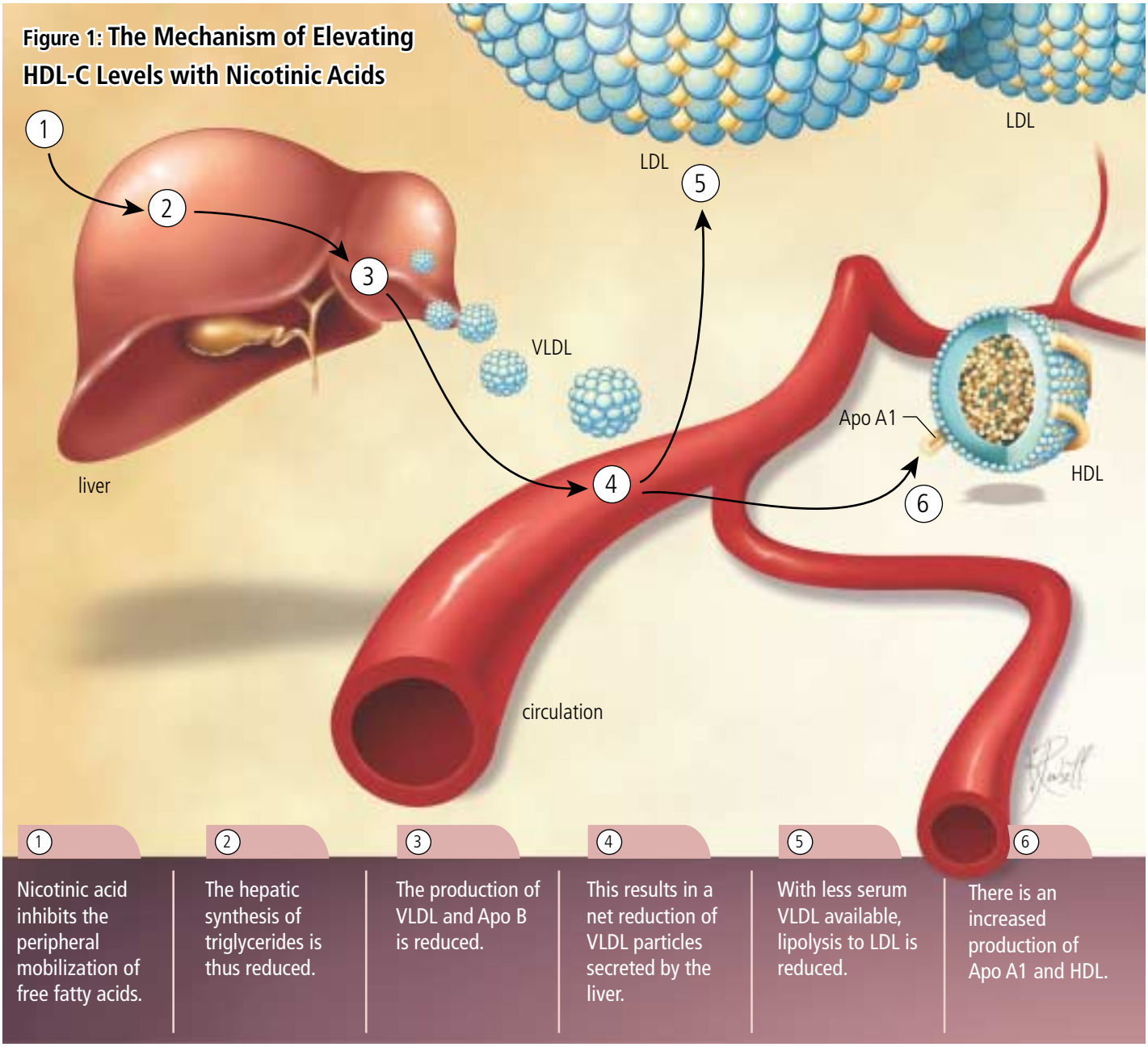
Exercise

A meta-analysis of 52 exercise training trials of > 12 weeks duration, including 4,700 subjects, demonstrated an average increase in HDL-C levels of 4.6% and reductions in triglyceride and LDL-C concentrations of 3.7% and 5.0%, respectively.[13] Data from the Ochsner Clinic Foundation group has shown a 6–16% increase in HDL-C with cardiac rehabilitation and exercise training programs in older patients with CAD, including patients 75 years or older.[14,15] Likewise, Rubinstein, *et al.* described 10% and 33% improvements in HDL-C in healthy military recruits without CAD after six and 12 weeks, respectively, of intense exercise training.[16] Despite the idea that patients with low HDL-C and hypertriglyceridemia have a greater HDL-C response to non-pharmacologic therapy,[15] some studies have demonstrated similar or less remarkable improvements in HDL-C when compared to patients with low HDL-C and normal triglyderides.[17,18] Smoking cessation not only increases HDL-C but also independently reduces the risk of CAD.[19-21]

Patients with CAD

The effect of combined non-pharmacologic measures on HDL-C in patients with CAD was evaluated in a study done

Figure 1: The Mechanism of Elevating HDL-C Levels with Nicotinic Acids

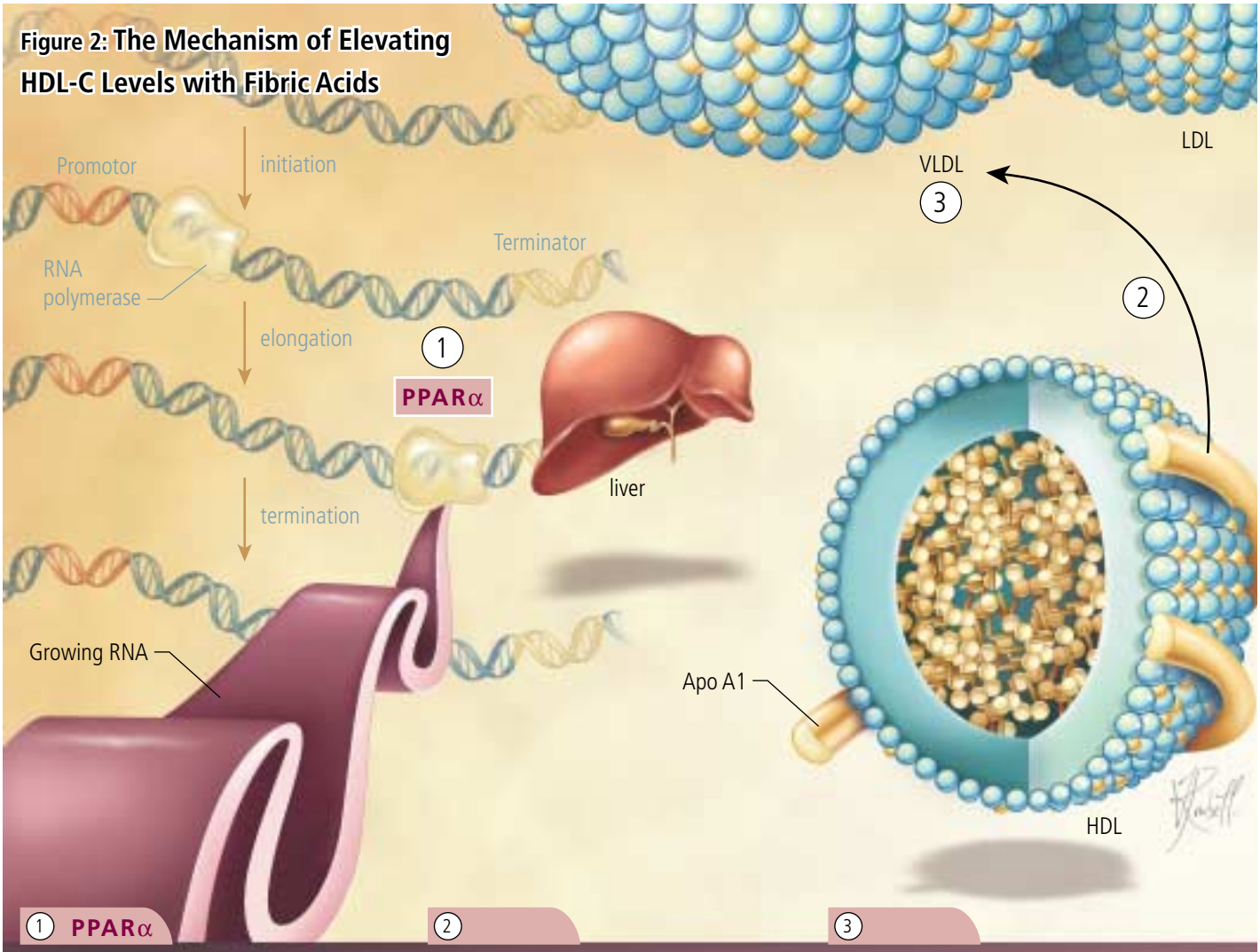


at two major institutions with cardiac rehabilitation units.[22] The effect of aggressive hygienic interventions (AHA/NCEP phase I diet, directly supervised exercise program, weight loss and smoking cessation program) on isolated low HDL-C was evaluated and compared to the effect on high LDL-C and on non-isolated low HDL-C. Despite achievement of similar reduction on other risk factors, the effect on HDL-C was more significant in patients with isolated low HDL-C (+17% versus +2%, $p < 0.001$), and there was a non-significant change in LDL-C. This study suggested that patients with isolated low HDL-C are sensitive to hygienic measures and gain important benefit from this therapy.

Estrogen Replacement Therapy

Estrogen replacement therapy is known to cause favourable effects on lipids because it raises HDL-C levels by 7–16%, and lowers LDL-C by 15–25%,[23] as well as significantly lowers lipoprotein (a) [Lp (a)]. However, estrogens also raise triglycerides which may be associated to small LDL particles,[24] can increase inflammatory markers and may cause coagulation abnormalities that adversely affect the incidence of cardiovascular disease.[25] Therefore, initiation or continuation of estrogen therapy is not recommended for the treatment of low HDL-C. However, in the HERS trial, women with Lp (a) > 25mg/dL had significant mortality benefit with hormone replacement therapy, although the results in the rest of the

Figure 2: The Mechanism of Elevating HDL-C Levels with Fibric Acids



trial were very disappointing. For this reason, estrogen therapy could be considered for women with CAD who have elevated Lp (a), more so if they also have low HDL-C and normal triglycerides.

Pharmacologic Treatment of Low HDL-C

In our experience, many patients with low HDL-C levels have an inadequate response to non-pharmacologic therapy. Pharmacologic therapy is recommended for high-risk patients who are not responding to non-pharmacologic interventions or who have persistently low HDL-C after treatment of other coexistent lipid abnormalities (especially if there is evidence of CAD).[26] The available pharmacologic options include fibrates, nicotinic acid and the combination of an LDL-lowering drug with either a fibrate or nicotinic acid.

Optimal drug therapy of low HDL-C is determined in part by the presence or absence of other lipid abnormalities.[11]

Low HDL-C and High LDL-C

In patients who also have high LDL-C, the primary target of therapy is LDL-C; this goal should be reached (usually with a statin) before treating low HDL-C. If HDL-C remains low, it can be effectively treated with either nicotinic acid or fibrates. However, combination of a statin with a fibrate (especially gemfibrozil, since fenofibrate is associated with far fewer drug interactions) should be care-

fully used because of the increased risk of myopathy. In this setting, pravastatin or fluvastatin may be the statins of choice because they have fewer drug interactions and perhaps less intrinsic muscle toxicity than other statins that are more lipophilic and that undergo more metabolism by the cytochrome P450 3A4 system. In general, however, the interaction of nicotinic acid with statins is relatively uncommon.

Low HDL-C and Hypertriglyceridemia

When low HDL-C is accompanied by hypertriglyceridemia (with normal or minimally elevated [< 130mg/dL] LDL-C), monotherapy with fibrates or nicotinic acid may be sufficient to correct both abnormalities and non-HDL-C levels should be corrected. In this setting, nicotinic acid and fenofibrate usually lower LDL-C considerably better than does gemfibrozil. If LDL-C levels are still minimally elevated after the hypertriglyceridemia is reversed, a statin can be added.

Isolated Low HDL-C

For high-risk patients (with CAD or CAD-equivalents) with isolated low HDL-C levels (without any other lipid abnormality), nicotinic acid is the most effective therapy. For high-risk patients who cannot tolerate nicotinic acid, statin therapy can be considered.

Nicotinic Acids

Niacin is the most effective medication for raising isolated low HDL-C, raising HDL-C by as much as 30–35% (about two- to three-fold more than fibrates). Niacin inhibits the hepatic synthesis of VLDL, reduces the transfer of cholesterol from HDL-C to bery low-density lipoprotein (VLDL) and delays HDL-C clearance (Figure1).[27] In one study of 37 patients with isolated low HDL-C, nicotinic acid (in a mean dose of 4.5g/day) raised serum HDL-C by 30% versus only 10% with gemfibrozil.[28] In another study, an extended-release niacin at higher doses provided up to two-fold greater HDL-C increases, (in addition to greater reduction of Lp (a), improvements in HDL-C/cholesterol ratios and lower fibrinogen levels) compared with gemfibrozil.[29] Gemfibrozil, on the other hand, gave a greater triglyceride reduction but also increased the LDL-C level, which did not occur with extended-release niacin. We have reported the marked benefit of sustained release niacin in patients with isolated low HDL-C, with even more remarkable improvement in those with concomitant hypertriglyceridemia.[30] The combination of niacin and simvastatin in the HATS trial was noted to produce marked benefit on improving both LDL-C (-42%) and HDL-C (+26%), as well as reducing CAD progression, stimulating CAD regression and producing marked (nearly 90%) reduction in CAD events.[31] Furthermore, a recent study demonstrated the effect of niacin for improving the reduced forearm blood flow in patients with atherosclerosis.[32] This improvement in endothelial function was directly proportional to niacin-induced increase in HDL-C.

In those patients with very low levels of HDL-C or who do not respond to single-agent therapy, the combination of gemfibrozil and nicotinic acid is more effective than monotherapy, raising HDL-C by as much as 45%.[33]

Fibric Acids

Fibric acids contribute to the elevation of HDL-C levels through three mechanisms:

1. Direct stimulation of the synthesis of HDL apolipoproteins A-I and A-II, by stimulating the activity of the liver transcription factor PPAR that increases the transcription of Apo-A-I mRNA and Apo-A-II mRNA.
2. Increased transfer of Apo A-I and other surface components in conjunction with diminished cholesterol transfer from HDL to VLDL.
3. Less inhibition by VLDL (due to the reduction in concentration) of hepatic Apo A-I synthesis (Figure 2).

The effect of fibric acids (fibrates) has been studied in primary and secondary prevention trials with beneficial results in terms of prevention of CAD events (BIP, VA-HIT and Helsinki Heart trials).[34-36] Fibrates are the first-line therapy in those patients who have low HDL-C associated with hypertriglyceridemia or as an alternative to niacin in patients with isolated low HDL-C (in presence of CAD). They are well known for their effect of reducing triglycerides by up to 60%, but they also increase HDL-C by 10–15%. Their effect on LDL-C is minimal, and particularly with gemfibrozil at a dose of 600mg twice daily, HDL-C levels increase by an average of 11%. However, the Helsinki Heart Study showed a more prominent elevation in HDL-C in those patients at greatest cardiovascular risk, and subgroup analysis found that gemfibrozil was particularly effective in preventing heart disease in patients with high serum triglycerides plus either low HDL-C or a high LDL/HDL cholesterol ratio (> 5.0).[7] The VA-HIT trial included 2,531 patients with CAD who had an LDL-C ≤ 140mg /dL an HDL-C ≤ 40mg/dL, and triglycerides ≤ 300mg/dL; the patients were randomly assigned to treatment with gemfibrozil or placebo. At five years, the combined primary endpoint of cardiac death and nonfatal myocardial infarction occurred less often in the gemfibrozil group (17.3% versus 21.7% for placebo). Multivariate analysis of the VA-HIT trial found that the reduction in nonfatal myocardial infarction and CAD death was strongly correlated with the serum HDL-C concentration achieved with gemfibrozil therapy, but was independent of changes in LDL-C or triglycerides. Slow release fibrates (fenofibrate) have been found to be more effective than gemfibrozil, for increasing HDL-C beyond the levels achieved with the latter medication, and being effective even in those patients not responding to gemfibozil; in addition, they provide much better effect than gemfibrozil for lowering LDL-C.[37]

Statins

Statins have been traditionally less effective in raising HDL-C; generally the start-

ing doses of statins increase HDL-C by 5–7%. However, there is evidence that simvastatin at high dose (40–80mg/day) appears to be more effective than atorvastatin (20–40mg/day) in raising serum HDL-C and apolipoprotein A-I concentrations (9.1% versus 6.8%, p <0.001 and 5.6% versus 2.6%, p <0.001, respectively).[38,39] Rosuvastatin, a new hydroxymethylglutaryl CoA reductase inhibitor, seems to be even more effective in raising HDL-C. Rosuvastatin at doses of 5 and 10mg compared with atorvastatin 10mg was found to cause greater increase in HDL-C (13% and 12%, respectively, versus 8%; p <0.01 and p <0.05, respectively) in addition to producing greater reductions in LDL-C (-40% and -43%, respectively versus 35%; p < 0.01 and p < 0.001, respectively). Apolipoprotein A-I increments were also greater with rosuvastatin, while triglyceride reductions were similar.[40] In addition, several trials have demonstrated that statin therapy is associated with marked clinical event reduction even in patients with low levels of LDL-C.

Conclusion

In conclusion, substantial data support the importance of HDL-C as a risk factor and therapy to increase levels of HDL-C in most subgroups, including moderate- and high-risk older cohorts with both non-pharmacologic (especially weight loss and aerobic exercise) and pharmacologic approaches (niacin, fibrates and statins).

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Dr. Milani has acted as a consultant and speaker for Bristol-Myers Squibb, Merck and AstraZeneca.

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