New Developments in the Treatment of Low High-Density Lipoprotein Cholesterol

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Reduced levels of high-density lipoprotein (HDL) cholesterol represent an important risk factor for the development and progression of coronary artery disease. In recent years, clinical outcome studies have verified that statin therapy may reduce the risk of initial or recurrent cardiovascular events in subjects with elevated or "normal" cholesterol levels. Subgroup analysis has also revealed that patients with low HDL benefit from this therapy. Two recently presented outcome trials using fibrate therapy also demonstrated a potential role for these medications in subjects with low HDL. The use of various HDL raising agents, singly or in combination on arteriographic progression and their potential mechanisms of action are reviewed. The latter may be an important consideration in the treatment of high-risk patients with low HDL.

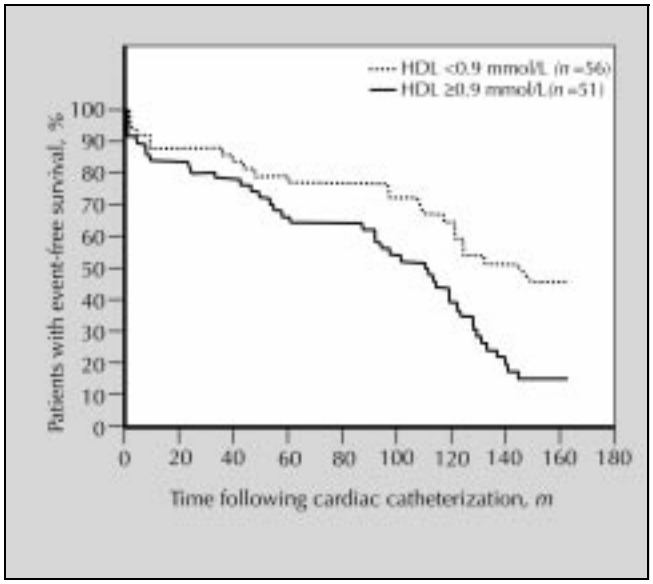

Figure 1. Kaplan-Meier survival analysis comparing coronary artery disease patients with desirable total cholesterol and baseline high density lipoprotein (HDL) < 0.9 mmol/L or ≥ 0.9 mmol/L. Peto and Peto's log-rank test indicates significant differences in event-free survival between the groups. Z=-2.80; *P*=0.005.

Introduction

Low levels of high-density lipoprotein cholesterol (HDL-C) are frequently encountered in subjects at increased risk for coronary artery disease (CAD) [1]. Even when total cholesterol levels are considered desirable (*eg*, <200 mg/dL; 5.2 mmol/L), low HDL is highly prevalent in patients with CAD and doubles the risk of future cardiovascular events (Fig. 1) [2,3]. Despite provocative observational studies, clinical trial data is limited. In the Helsinki Heart Study [4], subjects with the lowest baseline HDL-C evidenced the greatest decrease in initial CAD events. More recently, clinical trials have evaluated the impact of raising HDL in patients with preexisting CAD with and without reduced HDL-C. The new studies provide compelling evidence that CAD progression and cardiovascular event rates may be favorably influenced in subjects with low HDL-C. This review highlights these recent clinical trials and discusses the cardioprotective mechanisms ascribed to raising HDL.

Recent Clinical Trials Evaluating Low High-Density Lipoprotein Concentrations

Fibrate therapy for low high-density lipoprotein concentration

Two recently completed secondary prevention trials evaluated the impact of fibrates in patients with reduced HDL-C. Both of these studies were presented in 1998 and are expected to be published later this year.

Bezafibrate infarction prevention trial

The Bezafibrate Infarction Prevention Trial (BIP) was a multicenter trial of men and women ages 45 to 75 years with documented CAD [5]. Previously, bezafibrate had been evaluated in the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) study [6]. This 2-year arteriographic study of young (<45 years) male survivors of myocardial infarction found reduced arteriographic progression in bezafibrate treated patients. Beneficial alterations in HDL-C

(> 9 %; $P = 0.02$), triglycerides (TG) (< 31%; $P < 0.001$), and fibrinogen (12%; $P = 0.001$) were observed without changes in low-density lipoprotein (LDL-C), suggesting that the improvement observed with bezafibrate was independent of LDL-C reduction. The BIP study therefore sought to determine whether bezafibrate also favorably reduces cardiovascular event rates. The results of the BIP study were presented at the European Atherosclerosis Society Meeting in Vienna, Austria (August, 1998). The lipid altering effects included significant increases in HDL-C (10%) and reductions in TG (25%) without significant lowering of LDL-C (5%). There was an insignificant (9%) reduction in the primary endpoint, nonfatal myocardial infarction (MI), and sudden cardiac death. A post-hoc analysis in bezafibrate-treated patients with TG more than 200 mg/dL ($n = 459$); however, revealed a 40% reduction in the primary endpoint ($P = 0.03$). The Veterans Affairs HDL Intervention Trial (VA-HIT) was a 5-year randomized controlled study of male Veterans less than 74 years of age with preexisting CAD. The eligibility criteria was similar to BIP, except a lower cutpoint for LDL and HDL was employed (Table 1). The results of this trial included increases in HDL (7.5%) and reductions in TG (24.5%), which translated into significant reductions (22%) in the primary endpoint, nonfatal MI and cardio-vascular death ($P = 0.006$). Significant reductions in transient ischemic attack (TIA) (40%; $P = 0.001$) and stroke (26%; $P = 0.05$) were also observed. The relative contribution of TG lowering and HDL raising on CAD event rate will be determined in this study. The divergence in results between the VA-HIT and BIP trials may in part be explained by the population studied and associated baseline characteristics. In both the VA-HIT and BIP trials, HDL levels were low; in BIP, the entry criteria for LDL were considerably higher. A comparison between baseline characteristics in BIP and VA-HIT [7] is shown in Table 2. All patients in VA-HIT were men and 70% were older than the mean baseline age of the BIP study (60 years). In addition to an increased prevalence of smokers, there were also more patients with CAD and diabetes mellitus, hypertension, and obesity suggesting a higher prevalence of Syndrome X in VA-HIT than in BIP. Indeed, there was a considerably higher event rate in placebo treated patients in VA-HIT study (21.1% compared with 14.9% in the BIP study). The preliminary results of these clinical endpoint trials suggest that raising HDL and lowering TG with fibrate therapy may reduce CAD event rates in normocholesterolemic patients with low HDL and elevated TG (especially >200 mg/dL). Additionally, the results of angiographic trials are extended, which demonstrated reduced progression of CAD in men with low HDL [6,8•]. What remains unanswered, however, is the relative efficacy of fibrate therapy compared with statins on CAD event rates in patients with low HDL and elevated TG. A number of ongoing clinical trials employing fibrates, either singly or in combination with fibrates should aid to further define the patients groups most likely to benefit from this therapy.

Table 1. Eligibility Criteria and Mean Baseline Levels of Lipids and Lipoproteins in Bezafibrate Infarction Prevention (BIP) and VA-HDL Intervention Trial (HIT)

BIP, mg/dL	HIT, mg/dL
LDL	
< 180	< 140
(148)	(111)
HDL	
< 40	< 35
(32)	(35)
TG	
< 300	< 300
(161)	(149)
TC	
(212)	(175)

BIP— Bezafibrate Infarction Prevention; HIT— VA-HDL Intervention Trial; LDL— low-density lipoprotein; HDL— high-density lipoprotein; TC— total cholesterol; TG— triglyceride

Table 2. Selected Baseline Characteristics in the Bezafibrate Infarction Prevention (BIP) Trial and the VA-HDL Intervention Trial (HIT)

	BIP	HIT
Number	31,222	531
Men, %	91	100
Age, yrs	60	64
BMI, kg/m^2	27	29
Diabetes, %	10	25
HTN, %	32	57
Smokers, %	11	21

BMI—body mass index; HTN—hypertension

Statin therapy for low high-density lipoprotein

Primary prevention trials

Two primary prevention studies employing statin therapy have provided evidence that patients with low HDL may benefit from this therapy. The West of Scotland Coronary Prevention Group (WOSCOPS) evaluated nearly 6000 hypercholesterolemic (mean TC = 272 mg/dL) middle-aged (45 to 64 years) men with no prior history of MI [9]. Patients receiving pravastatin (40 mg) experienced significant reductions in LDL (26%) and TG (12%) with increases in HDL (5%). These favorable alterations were associated with significant reductions (31%) in the primary endpoint, CAD death, and nonfatal MI. Pravastatin-treated men with baseline HDL levels below the median (43 mg/dL) experienced similar reductions in the primary endpoint as men with HDL above the median (31% vs 33%). More recently, these findings were tested in normocholesterolemic men and women who participated in the Air Force-Texas Coronary Artery Progression Study (AFCAPS/TEXCAPS) [10•]. This primary prevention study investigated the impact of lovastatin in middle-aged men (> 45 years) and women (> 55 years) with low HDL concentra-

tions(< 50 mg/dL). Subjects assigned to lovastatin (20 mg/d titrated to 40 mg/d to achieve LDL < 110 mg/dL) evidenced significant reductions in LDL (25%) and TG (15%) and significant increases in HDL (6%). These lipid altering effects translated into reductions in initial major coronary events (37%; $P < 0.001$) and fatal or nonfatal MI (40%; $P = 0.002$). As in WOSCOPS, subjects with low baseline HDL benefited from therapy. In fact, event rate reduction was most noteworthy in subjects with baseline HDL less than 40 mg/dL, compared with higher HDL levels.

Secondary prevention trials

The 4S study, which evaluated simvastatin in hypercholesterolemic (mean TC = 261 mg/dL) patients with preexisting CAD reported a 30% reduction in total mortality and a 42% reduction in recurrent CAD events [11]. In this study, subjects assigned to simvastatin (20 mg/d titrated to 40 mg/d) evidenced significant reductions in LDL (35%) and TG (10%) with increases in HDL (8%) . Patients with HDL at the lowest quartile (< 40 mg/dL) evidenced a 33% reduction in CAD events, which was not materially different compared with the benefit observed at higher HDL quartiles [12]. These results support the benefit of LDL lowering in hypercholesterolemic patients with CAD, even with reduced HDL. Similar results were obtained in the Long Term Intervention with Pravastatin in Ischaemic Disease (LIPID Study) [13]. In this study of more than 9000 men and women with preexisting CAD but with cholesterol levels more representative of patients with CAD than 4S (mean TC = 218 mg/dL), there were significant reductions in LDL (25%) and TG (11%) with increases in HDL (5%). These results coincided with reductions in cardiovascular and total mortality (25% and 22%, respectively). In the prespecified analyses of HDL, patients with baseline HDL of less than 39 mg/dL exhibited similar reductions in CAD death and nonfatal MI (24%) as those with baseline HDL of at least 39 mg/dL.

Arteriographic trials

In addition to the BECAIT [6] study listed above, the Lipid Coronary Angiography Trial (LOCAT) [8•] investigated the use of fibrate therapy on arteriographic progression of CAD. Middle-aged men who had coronary artery bypass grafting were primarily selected if they had low HDL (mean = 40 mg/dL). They were randomized to placebo or gemfibrozil (1200 mg/d) for 32 months followed by coronary arteriography. At baseline, participants had desirable TC (200 mg/dL) and TG (140 mg/dL) with increased LDL (134 mg/dL) and low HDL (40 mg/dL). Fibrate treated subjects evidenced significant elevations in HDL (9%) and reductions in TG (40%). Despite the modest reductions recorded for TC (9%) and LDL (6%), arteriographic progression was significantly reduced in gemfibrozil treated patients. The most important predictors of advancing disease in this study were TG-rich lipoproteins, most notably intermediate-density lipoprotein (IDL) and the HDL3 subfraction. As in the BECAIT study, the combination of HDL raising and TG lowering rather than LDL reduction were most influential in the favorable arteriographic changes observed.

The impact of arteriographic progression in patients with low HDL was recently assessed with statin therapy. The Lipoprotein and Coronary Atherosclerosis Study (LCAS) [14] evaluated the effect of fluvastatin sodium in men and women ($n = 429$) with arteriographic CAD and mild to moderate elevations in LDL (mean = 160 mg/dL). Patients were placed on fluvastatin sodium 40 mg/d (plus cholestyramine if mean baseline LDL > 160 mg/dL) or placebo with follow-up angiography at 2.5 years. Significant changes in lipids and lipoproteins were observed with the most marked reductions in TC (18.1%) and LDL (26.5%). This translated into significant reductions in minimum lumen diameter between baseline and follow-up arteriogram. Further analyses were recently performed to compare arteriographic progression in subjects with and without low HDL at baseline [15•]. Compared with placebo, fluvastatin sodium significantly reduced arteriographic progression in patients with low HDL (< 35 mg/dL) (Fig. 2). In the post-coronary artery bypass graft (post-CABG) Trial [16]. Aggressive treatment with lovastatin (40 to 80 mg/d + cholestyramine 8 g/d), eliminated most of the enhanced risk in subjects with reduced HDL. These results are consistent with the beneficial effects observed in the clinical endpoint studies described above (Fig. 3). Thus, although statins have not been viewed as powerful HDL raising agents, there may be other important effects that may contribute to the marked benefit noted in patients with reduced HDL.

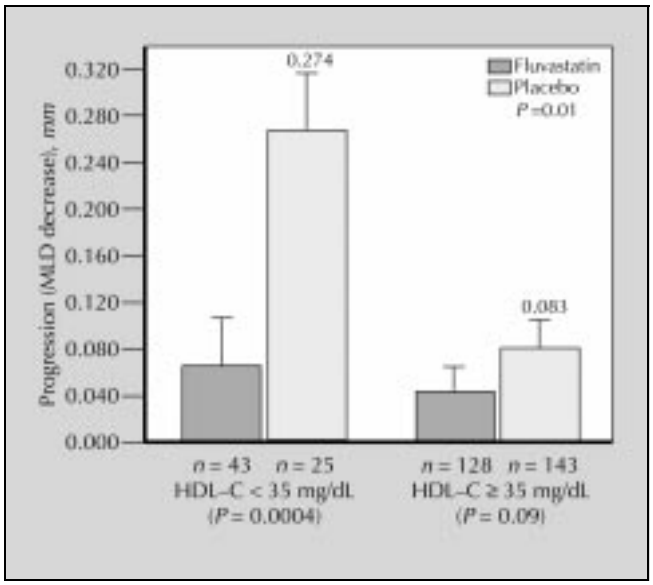

Figure 2. Among patients with low–HDL-C those being treated with fluvastatin had significantly less CAD progression measured by MLD change (mean±SE). The difference between change in MLD in fluvastatin and placebo low HDL-C patients was significantly greater than in higher HDL-C patients as assessed by the interaction of treatment and HDL-C category.

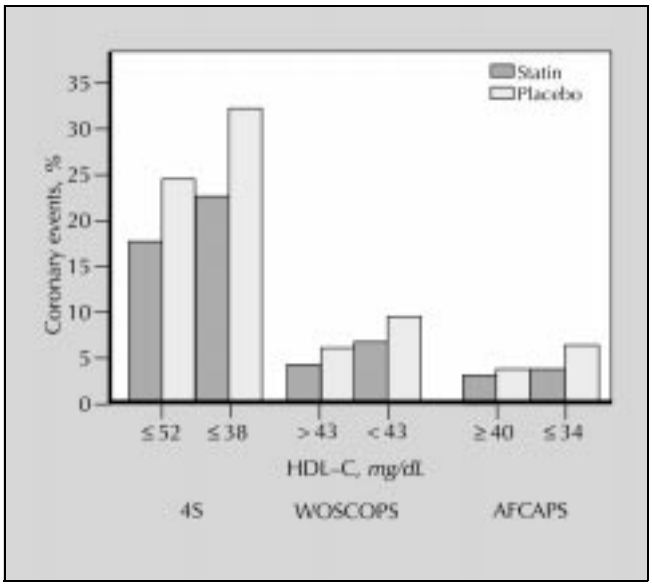

Figure 3. Statin therapy for patients with low–HDL-C reduces coronary risk to approximately that of patients with high HDL-C on placebo. 4S Scandinavian Simvastatin Survival Study (highest and lowest quartiles); AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study (highest and lowest tertiles). WOSCOPS—West of Scotland Coronary Prevention Study (at or above the median versus below the median).

High-density lipoprotein-raising effect and potential mechanisms of pharmacologic agents

Statins

All statins raise HDL, although the impact is often modest (5%–10%) as illustrated in the clinical endpoint studies cited above. Similar to a heightened effect with high TG (*eg*, > 200 mg/dL), statins also appear to influence HDL in subjects with the lowest levels more profoundly. For example, one very recent study observed that simvastatin (80 mg/d) raised HDL approximately 18% in subjects with HDL less than 35 mg/dL compared with 5% if HDL levels were higher. The HDL increase with Atorvastatin (40 mg/d) was also higher in subjects with HDL less than 35 mg/dL compared with HDL less than 35 mg/dL (13% vs 6%). In addition, levels of apolipoprotein (apo) AI, the primary apolipoprotein of HDL, were also higher in the simvastatin treated group [17]. The clinical implications of these findings are presently unknown.

In addition to the LDL-lowering benefits that contribute to plaque stabilization and restoration of endothelial function, there may be additional benefits attributed to statin use in patients with low HDL. Principal among these is inhibition of LDL oxidation [18], which may be particularly important in patients with low HDL who may also be subjected to reduced paraoxynase, an HDL glycoprotein that reduces LDL oxidation [19]. In addition, apoAI bears structural homology to prostacyclin-stabilizing factor [20]. As statins have also demonstrated antithrombotic effects [21], patients with low HDL who receive this medication may be at reduced risk of arterial thrombosis.

Fibrates

Fibrates activate the peroxisome proliferator activator receptor (PPAR). The activation of PPAR results in upregulation of lipoprotein lipase transcription, thereby enhancing TG-rich lipoprotein hydrolysis and facilitating the transfer of surface components to nascent HDL. Activation of PPAR also results in the downregulation of apolipoprotein C3, which inhibits LPL. On average, fibrates lower triglycerides 20% to 40% and raise HDL 10% to 20%. In the Helsinki Heart Study [4,22], for each 1 mg/dL increment in HDL, the risk of an initial CAD event was reduced 2% to 3%; the greatest rise in HDL was observed in patients with the lowest levels at baseline (< 35 mg/dL).

Niacin

Niacin is the most powerful of the HDL raising agents. The immediate release (IR) form may raise HDL levels to a slightly greater extent than the slow release (SR) preparation. On average, niacin raises HDL 10% to 30% with most of the rise in the HDL2 fraction. Niacin reduces hepatic very low-density lipoprotein (VLDL) production and lowers both fasting and postprandial TG [23]. Both the IR and SR preparations have been implicated in hepatotoxicity. Fulminant hepatic necrosis has been reported more commonly with the SR preparation. This may reflect over the counter preparations that were under poor quality control or its improper use (*eg*, 3–4 times daily). A new SR preparation appears to be safe and without reports of irreversible hepatotoxicity or rhabdomyolosis [24].

Other high-density lipoprotein-raising agents

There are other agents that raise HDL (10%–20%). Alcohol raises HDL (predominantly HDL3) but also increases TG. Estrogens raise both HDL (primarily HDL2) and TG by inhibiting hepatic lipase; a putative proatherogenic lipolytic enzyme [25••]. Other HDL raising agents include sympathomimetic agents which enhance lipoprotein lipase (LPL) activity, such as beta adrenergic receptor agonists (*eg*, terbutaline sulfate); a1-adrenergic inhibitors also raise LPL, thereby lowering TG and raising HDL [26]. Anticonvulsants (*eg*, phenytoin) also raise HDL, with predominant elevation of the HDL2 subfraction [27]. The clinical implication of HDL raising with these agents is unknown and it has not been established whether HDL subfractions refine cardiovascular risk assessment to a greater extent than total HDL measurements.

Combination therapy

Combination therapy employed in earlier arteriographic studies have demonstrated marked improvement in HDL. For example in the Cholesterol Lowering Atherosclerosis Study (CLAS) [28], dietary modification in combination with the bile acid resin, cholestyramine, and niacin resulted in HDL increases of 37%, LDL reduction of 43%, and 25%

Table 3. Evidence Based Approach to the Treatment of Low High-Density Lipoprotein (< 35 mg/dL) and Coronary Atery Disease

LDL > 130 mg/dL	LDL: 100 – 130 mg/dL	
TG > 200	TG < 200	> 200
Statin	Statin	Statin or Fibrate
	Fibrate	
Therapies Not Established		
Combination: Statin + Niacin or fibrate		
Statin + omega-3 compounds		

LDL—low-density lipoprotein; TG—triglycerides

reduction of cardiovascular events. In the Familial Atherosclerosis Treatment Study (FATS) [29], a similar combination resulted in a 43% increase in HDL and was associated with greater arteriographic regression compared with other treatment groups. In smaller scaled nonclinical endpoint studies, combination of niacin (immediate release and sustained release) and statins have resulted in up to 36% increases in HDL [30]. Importantly, of the nearly 500 patients treated, there were no cases of myositis reported [24]. The combination of statin (simvastatin, 10 mg, or pravastatin, 20 mg) and fenofibrate tested in 80 patients disclosed a 22% increase in HDL . There were no cases of serum asparate aminotransferase/serum alanine aminotransferase that were three times the upper limits of normal myositis reported [31]. These data suggest that combination therapy is a safe and effective therapy for raising HDL.

Treatment Algorithm for Pharmacologic Treatment of Low Levels of High-Density Lipoprotein

An approach to treating patients with low HDL and CAD is presented in Table 3. Because of their proven efficacy, statins are the first line of therapy in hypercholesterolemic patients (LDL > 130 mg/dL) with low HDL, with or without elevated TG (> 200 mg/dL). Although the data are less convincing, statins may also be considered as the first line of therapy even when LDL levels range between 100 and 130 mg/dL. Although no benefits of LDL lowering were apparent with baseline levels below 125 mg/dL in the post-hoc analysis in the CARE study, the larger LIPID study, which compared LDL tertiles in the prespecified subgroup analysis, observed reduced but not statistically significant differences in CAD events in subjects at the lowest tertile LDL (< 135 mg/dL), compared with higher tertiles at baseline [31]. Although the impact of low HDL within the low LDL subgroup has not been reported, the lack of CAD event rate differences between low and high HDL subjects overall, suggest that statin therapy would be a worthy consideration in this group. With regard to fibrate use, the VA-HIT study found that gemfibrozil was useful in patients with CAD, with low HDL, LDL (100–130 mg/dL), and TG (200 mg/dL). The BIP study also demonstrated reduction in CAD events with fibrate therapy, but the benefit was limited to patients with TG of less than 200 mg/dL. Thus, fibrate therapy appears to be a suitable alternative to statins in this subgroup. However, they remain second line agents in patients with LDL of less than130 mg/dL, because of the overall negative results of the BIP study. Niacin remains a second line agent in patients with CAD and low HDL because of the lack of clinical endpoint trials evaluating these parameters. In the Coronary Drug Project [32], there was a 27% reduction in recurrent, nonfatal MI during the 5-year study associated with a 9.9% reduction in total cholesterol and 26.1% reduction in TG (HDL levels were not measured). The improvement in total survival observed 9 years following its discontinuance, suggests that niacin may exert long-term benefits [33]. Similarly, a recently completed Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 (GISSI) substudy presented at the 1999 American College of Cardiology Scientific Sessions observed improvement in overall survival among subjects receiving 1 gram of omega-3 fatty acids (Omacor®, Norway) daily. Again, the impact of these agents in patients with low HDL have yet to be assessed. Finally, there is strong suggestion from arteriographic data that combination therapy is effective in reducing arteriographic progression and raising HDL; the results of ongoing outcome trials should aid in providing further reassurance of the efficacy and safety of these therapies.

Future Directions for Treating Low Levels of High-Density Lipoprotein Concentration

Gene therapy

The use of gene therapy as a potential target for raising HDL has received considerable attention in recent years. Overexpression of apoAI, the primary apo of HDL was shown to reduce atherosclerotic lesions in transgenic mice [34]. More recently, expression of a human apoAI transgene using the Rous sarcoma virus in human apoAI transgenic mice resulted in prolonged (10-week) concentrations of HDL and apoAI that were associated with reduction in fatty streak lesion formation [35•]. In addition to apoAI, overexpression of lecithin-cholesterol acyltransferase has also been associated with prevention of diet-induced atherosclerosis in rabbits [36]. Although early results are encouraging, issues that require further evaluation include enhancement of long-term viral promoter expression and reduction in immunogenicity. Once such impediments are removed, clinical studies using gene therapy in HDL deficiency states should be forthcoming.

Conclusions

Primary and secondary prevention studies support a role of statin therapy for the treatment of low HDL. Recent data

also indicate that low HDL patients without elevated LDL may benefit from fibrate therapy, particularly if TGs are also elevated. The modest rise in HDL with these agents may be amplified with combination therapy and ongoing clinical outcome trials will determine the impact of this modality. Future targets for HDL raising including gene therapy, which may be a particularly useful approach in subjects with familial deficiency of one or more candidate genes, involved in the metabolic regulation of HDL.

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Study of 395 men with low HDL (< 43 mg/dL or 1.1 mmol/L) and moderately elevated LDL (< 175 mg/dL or 4.5 mmol/L) who had coronary artery bypass grafting and were assigned to gemfibrozil (1200 mg/d or placebo for 32 months). Comparison between initial and follow-up arteriogram revealed significant reduction in formation progression of saphenous vein graft lesions with medication. These results suggest that men with low HDL and CAD benefit from fibrate therapy even without markedly elevated LDL.

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This analysis from the LCAS study compared the impact of fluvastatin sodium in patients with low HDL (< 35 mg/dL) at baseline with subjects who have higher HDL levels. Significantly reduced arteriographic progression of CAD was observed in subjects with reduced HDL. These subjects also had the highest increases in HDL (16%) with drug therapy.

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