The American Journal of Medicine (2005) 118, 1067-1077

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THE AMERICAN JOURNAL *of* MEDICINE®

Review

Low HDL-C: A secondary target of dyslipidemia therapy

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KEYWORDS:
Cardiovascular disease;
Dyslipidemia;
High-density lipoprotein cholesterol

ABSTRACT: Current guidelines for the prevention of coronary heart disease (CHD) focus on lowering low-density lipoprotein cholesterol (LDL-C) as the primary target of lipid-modifying therapy. However, there is increasing interest in high-density lipoprotein cholesterol (HDL-C) as a secondary target of therapy. A wealth of epidemiologic data demonstrate that low levels of HDL-C are associated with an increased risk of CHD events, and data from large-scale clinical trials with statins and fibrates indicate that observed clinical benefits are related, at least in part, to improvements in HDL-C levels. Raising HDL-C levels with therapeutic lifestyle changes and pharmacologic intervention might afford opportunities to further reduce the risk of CHD beyond LDL-C lowering. Statins are first-line pharmacotherapy for dyslipidemia and can also improve HDL-C levels, although the extent to which they modify HDL-C varies. Combining a fibrate or niacin with statin therapy raises HDL-C more than a statin alone but might be associated with reduced tolerability and increased adverse reactions. Several new therapeutic approaches to raising HDL-C are in development, including an HDL mimetic and inhibitors of cholesteryl ester transfer protein. Although lowering LDL-C remains the primary target of lipid-modifying therapy, dyslipidemia therapies that are efficacious for both LDL-C reduction and raising HDL-C might offer further improvements in CHD risk reduction.

It is widely accepted that reductions in cardiovascular morbidity and mortality are associated with decreases in plasma levels of low-density lipoprotein cholesterol (LDL-C). Indeed, guidelines for the prevention of coronary heart disease (CHD) focus on lowering LDL-C to defined levels,[1] and statins are recommended as first-line drug therapy because of their LDL-C lowering efficacy. Although CHD risk was reduced by 22-35% in statin trials, some patients still experienced coronary events despite significant lowering of LDL-C levels.[2] It has become clear that LDL-C forms only part of the overall clinical picture in individuals at risk of CHD and that it is necessary to consider other risk factors to explain the residual disease and premature death noted in the major statin trials.[2,3]

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doi:10.1016/j.amjmed.2004.12.021

In observational studies, plasma levels of high-density lipoprotein cholesterol (HDL-C) and its major protein, apolipoprotein A-I, have been shown consistently to be inversely correlated with CHD risk.[3] National Cholesterol Education Program guidelines do not identify HDL-C as a treatment target, but do, nevertheless, state that a level of HDL-C <40 mg/dL constitutes a risk factor for CHD, whereas a level ≥ 60 mg/dL is considered protective.[1] Recently, a working group reporting on low levels of HDL-C as a risk factor for CHD concluded that HDL-C is a rational target for cardiovascular therapy.[4] In addition, the American Diabetes Association recommendations on dyslipidemia management in adults with diabetes suggest that it might be appropriate to use pharmacologic therapy to raise HDL-C levels to >40 mg/dL in men and >50 mg/dL in women.[5]

In light of this increasing interest in HDL-C as a therapeutic target, this article will review the relationship between low HDL-C and CHD risk, the potential roles of

HDL-C in atherogenesis, and current and potential therapeutic options for raising HDL-C levels.

Relationship between low HDL-C and CHD

Prospective studies in several countries provide compelling evidence for an inverse relationship between levels of HDL-C and cardiovascular risk (Table 1).[6-16] This relationship has been quantified in an analysis of cohorts from 4 prospective North American studies.[17] Two of the cohorts were derived from purely observational studies (Framingham Heart Study and Lipid Research Clinics Follow-Up Study), and two from control groups of randomized trials in high-risk middle-aged men (Multiple Risk Factor Intervention Trial and Coronary Primary Prevention Trial). Incidence rates for CHD in each study were stratified according to high, intermediate and low HDL levels, and were consistently highest in the low HDL-C category and lowest in the high HDL-C category. The results from each cohort were consistent with a decrease of 2-3% in CHD risk for each 1 mg/dL increase in HDL-C level.[17] Another study examined the prevalence of risk factors in 321 men with angiographically documented CHD.[14] Nearly half the patients studied did not have elevated total cholesterol levels; however, 75% of participants with total cholesterol <200 mg/dL were found to have low HDL-C (<35 mg/dL). Indeed, low HDL-C was the second most common CHD risk factor (after smoking) in these patients.

It has been argued that low HDL-C should be considered a cardiac risk correlate rather than a direct treatment target, because it is seen in combination with other metabolic abnormalities, including elevated levels of triglycerides, a preponderance of atherogenic small LDL particles and high LDL particle numbers.[1,18] These lipid abnormalities are associated with the metabolic syndrome, a cluster of disorders that also includes abdominal obesity, hypertension, insulin resistance, and pro-inflammatory and pro-thrombotic states[19] and is linked in a highly significant manner to increased coronary risk.[20] However, most interesting in terms of the present discussion is the observation from the Scandinavian Simvastatin Survival Study in over 4000 patients that individuals with elevated LDL-C and triglycerides and low HDL-C are more likely than those with elevated LDL-C alone to have other characteristics of the metabolic syndrome and to be at increased cardiac risk.[21]

Analyses of data from other major prospective statin studies also provide evidence that a low HDL-C level contributes to CHD risk.[22,23] Although they were designed to focus primarily on LDL-C reduction, subsequent analyses demonstrated that the clinical benefit noted in these trials was not accounted for solely by effects on this lipoprotein fraction. For example, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study investigators found that 97% of the effect of pravastatin on the risk of fatal CHD, non-fatal myocardial infarction, unstable angina and coronary revascularization was explained by on-study lipid levels, with the combination of total cholesterol and HDL-C levels being among the most important lipid parameters associated with event reduction.[23]

HDL-C and atherogenesis

There are several mechanisms through which HDL-C may attenuate the formation and progression of atherosclerotic lesions, including its role in mediating reverse cholesterol transport. This process is promoted by apolipoprotein A-I and involves the transport and uptake of free cholesterol from peripheral tissues, such as the artery wall, with subsequent delivery to the liver for reuse or excretion into the bile.[24] Additional HDL-C properties demonstrated that might protect against atherosclerosis include anti-oxidant effects, attenuation of endothelial dysfunction, and anti-inflammatory effects. Particles of HDL provide anti-oxidant protection to LDL particles by scavenging reactive oxygen species.[25] Oxidized LDL contributes to the development of atherosclerotic lesions in several ways, including accumulation in macrophages to form foam cells and modulation of various pro-inflammatory pathways.[25] By preventing LDL oxidation, HDL-C may also prevent the associated inhibition of endothelial nitric oxide synthase.[26] Additionally, HDL-C may improve endothelial function by stimulating the release of prostacyclin, a vasoactive prostaglandin synthesized by vascular endothelial and smooth muscle cells.[27,28] In terms of anti-inflammatory effects, HDL-C might reduce cytokine-mediate upregulation of cell adhesion molecules and block the nuclear factor-κB signalling cascade.[29] However, pro-inflammatory actions of HDL-C have been demonstrated in a small study of men with CHD and high levels of HDL-C (>84 mg/dL).[30] This apparent paradox may derive from the preponderance of large HDL particles, which are less effective at free-radical scavenging, in individuals with high HDL-C levels.[31]

Interventions to raise HDL-C

A number of interventions are currently available for improving HDL-C profiles and thereby potentially reducing cardiac risk (Table 2).[32-45] These include therapeutic lifestyle changes and pharmacologic intervention with statins or fibrates as monotherapy or statins in combination with niacin. However, not all therapies that increase HDL-C reduce cardiac risk, as demonstrated for hormone replacement therapy in postmenopausal women.[46-48] There are several atherothrombotic effects of hormone replacement therapy that might act to offset the potential benefits of raising HDL-C and lowering LDL-C. For example, epidemiologic studies have reported significantly higher levels of C-reactive protein in women using estrogen alone or in combination with progestin[49,50]; elevated levels of C-reac-

Table 1 Prospective studies showing an association between HDL-C and cardiovascular risk

Study	n	Subjects	Follow up (years)	Main findings
The Oslo Study[6]	279	Men; 40-49 years; 89 subsequently developed CHD	Not applicable	Mean HDL-C level in patients who went on to develop CHD 7.9% lower than that of cohorts matched for smoking habits, triglycerides and total cholesterol
Donolo-Tel Aviv Prospective Coronary Artery Disease Study[7]	2935	Men and women; apparently healthy; 35-64 years	20	CHD events inversely related to the percent of cholesterol in HDL
Framingham Heart Study[8]	2748	Men and women; 50-79 years	12	Men; relative risk of CHD mortality = 4.1 in the lowest (<35 mg/dL) versus the top (>54 mg/dL) quintile Women; relative risk of CHD mortality = 3.1 in the bottom (<45 mg/dL) versus the top (>69 mg/dL) quintile
Israeli Ischemic Heart Disease Study[9]	10059	40-65 years	23	CHD mortality inversely related to the percent of cholesterol in HDL
Helsinki Heart Study[10]	2590	Men; Type IIa hyperlipidemia	5	In a population with elevated LDL-C, HDL-C was the lipoprotein fraction with the greatest value for predicting CHD
Miller et al[11]	960	Men; 35-69 years; free from CHD at entry	9	A low HDL-C concentration is a risk factor for CHD in non-whites as well as in whites
Lipid Research Clinics Prevalence Follow-up Study[12]	7569	Men and women; >30 years; no clinical CHD	8.4	Multivariate analysis revealed an inverse relationship between HDL-C levels and cardiovascular disease mortality in men and women after controlling for other risk factors
Pekkanen et al[13]	2451	Men; 40-69 years; 17% with evidence of cardiovascular disease at baseline	10.1	Hazard ratio for cardiovascular mortality was 6.02 for HDL-C <35 mg/dL relative to HDL-C ≥45 mg/dL for those with cardiovascular disease at baseline ($P<0.001$). This was also significant (although less pronounced) in men free from disease at baseline (2.83; $P=0.02$)
Genest et al[14]	321	Men; <60 years; angiographically documented coronary artery disease; not on lipid-lowering therapy	Not applicable	48% of patients with coronary artery disease had total cholesterol levels <200 mg/dL; 75% of those with total cholesterol <200 mg/dL had HDL-C <35 mg/dL The prevalence of HDL-C <35 mg/dL was markedly higher than in subjects in a control group of men with no evidence of coronary artery disease (63 vs 19%; $P<0.005$), whereas the prevalence of LDL-C ≥160 mg/dL did not differ between patients with coronary artery disease and those in the control group
Prospective Cardiovascular Münster Study[15]	4559	Men; 40-64 years	6.0	In univariate analysis, mean HDL-C was significantly lower in participants who developed coronary artery disease (39.5 mg/dL) compared with those who were free of coronary artery disease at the end of the follow-up period (45.2 mg/dL, $P<0.001$)
Québec Cardiovascular Study[16]	2177	Men; 35-64 years; 202 with known ischemic heart disease	Not applicable	Reduced HDL-C (<35 mg/dL) was more prevalent in men with known ischemic heart disease (50%) compared with those without IHD (30%). HDL-C remained a significant predictor of ischemic heart disease after adjustment for other risk factors

CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

Table 2 Summary of the effects of lifestyle and pharmacologic interventions on HDL-C

Intervention	Study reference	Details	Effects on HDL-C
Lifestyle			
Alcohol intake	Rimm et al 1999[32]	Meta-analysis of 36 data records including 886 adults from 25 studies (duration 1 week to 3 months)	Increase of 8.3% in an average individual consuming 30 g alcohol per day
	Hata & Nakajima 2000[33]	Meta-analysis of 24 publications including 26 712 men (all Japanese)	Increase of 0.06 mmol/L (3.9-9.5%) for every 23 g alcohol per day
Exercise	Leon & Sanchez 2001a and 2001b[34, 35]	Meta-analysis of 51 (including 28 randomized controlled trial) moderate intensity exercise training trials (>12-weeks duration) including 4700 participants	Average increase 4.6%
	Halbert et al 1999[36]	Meta-analysis of 31 studies including 1833 normo- and hyperlipidemic subjects	Increase of 0.05 mmol/L (3.3-6%) with aerobic and resistance exercise
Weight loss	Datillo et al 1992[37]	Meta-analysis of 70 studies involving diet-induced weight loss and lipid parameters	For every 1 kg decrease in body weight HDL increases by 0.009 mmol/L (0.58-1.08%)
	Yu-Poth et al 1999[38]	Meta-analysis of 37 dietary intervention studies (9276 subjects in intervention groups and 2310 subjects in control groups)	For every 1 kg decrease in body weight HDL-C increased by ~1%
Smoking cessation	Maeda et al 2003[39]	Meta-analysis of 29 cohorts from 24 studies (4476 patients)	Increase of 3.0-5.6% following smoking cessation
	Craig et al 1989[40]	Meta-analysis of 54 published cross-sectional studies.	HDL-C levels are 5.7% higher in non-smokers compared with smokers
Pharmacologic			
Statins	Edwards & Moore 2003[41]	Meta-analysis of 91 randomized controlled trial (43 404 patients on statins and 25 081 patients on placebo)	Increase 6-12% (3% with placebo)
Nicotinic acid	Goldberg 2004[42]	Meta-analysis from 5 randomized controlled trial in 432 patients with dyslipidemia treated with extended–release niacin (0.5 to 3.0 g) and compared with placebo	Increase 7.7-34.5%
Fibrates	Bowen & Guyton 2000[43]	Review	Increase 6-20%
	Rizos & Mikhailidis 2001[44]	Review	Increase 6-18%
Combination therapy	Brown et al 2001[45]	3-year, double-blind study in 160 patients on simvastatin plus niacin ±, anti-oxidant therapy, or placebo	Increase 26% with combination
	Bowen & Guyton 2000[43]	Review, statin and fibrate combination	Increase 17-22%
	Bowen & Guyton 2000[43]	Review, statin and niacin (immediate or extended-release) combination	Increase 14-28%

tive protein are clearly associated with increased cardiovascular risk in women.[51] There is also evidence that estrogens increase thrombin generation and impair fibrinolysis and raise very low-density lipoprotein triglyceride levels.[52]

Therapeutic lifestyle changes

Lifestyle changes recommended to reduce the likelihood of CHD. include smoking cessation, weight loss, exercise and diet, some of which have an effect on HDL-C levels.[1] In the Lipid Research Clinics Prevalence Study, smoking ≥20 cigarettes/day was shown to decrease HDL-C levels by 11-14% in a dose-dependent manner.[53] The same study also reported an inverse relationship between body mass index and HDL-C, with levels for patients in the 10th percentile for body mass index being 6-7 mg/dL higher than for those in the 90th percentile,[54] and a direct relationship between exercise and HDL-C levels was also observed.[55] A meta-analysis of more than 70 studies reported that, in general, HDL-C levels decreased during periods of active weight loss but increased again following weight stabilization.[56] Multiple regression analysis demonstrated an increase in HDL-C of approximately 2 mg/dL for every 4.5 kg weight reduction.[56,57] In a sample of 200 men enrolled in the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study, a significant increase in HDL-C level was seen in response to a 20-week endurance exercise program (4.9%; $P<0.005$) in men with high triglyceride (≥119 mg/dL) and low HDL-C (≤36 mg/dL) levels but not in those with low HDL-C in isolation.[58] Further data from a sample of 111 sedentary and overweight individuals with dyslipidemia showed greater benefit in terms of increased HDL-C levels with high levels of high-intensity exercise (9.7%; $P=0.015$) than with low amounts of exercise of moderate intensity (1.7%).[59]

Pharmacologic interventions

Several lipid-modifying drugs are known to have beneficial effects on HDL-C levels, including statins, fibrates and niacin. Collated data from a wide range of clinical trials indicated HDL-C increases in the order of 5-10% with statins, 10-15% with fibrates and up to 35% with niacin.[60] Of these, the statins are of foremost significance because they have been shown to reduce the risk of CHD in numerous prospective clinical trials regardless of entry LDL-C level[61,62] and are therefore recommended as first-line drug therapy for dyslipidemia.[1]

Evidence of the benefit of statin therapy for CHD prevention in patients with low HDL-C levels is available from several sources (Table 3). In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), treatment with lovastatin 20-40 mg/day decreased cardiovascular risk by 37% in subjects with average LDL-C and low HDL-C levels.[65] Lovastatin treatment resulted in HDL-C increase at 1 year of 6%, and subjects in the lowest two tertiles of baseline HDL-C experienced the greatest risk reductions.[66] By Cox regression analysis, LDL-C was predictive of an acute myocardial event only when HDL-C was included in the model. Similarly, in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study involving 5804 elderly men and women, the greatest benefit of treatment with pravastatin 40 mg/day was observed among subjects in the lowest tertile of HDL-C.[67] Assessment of the reduction in vascular events with simvastatin 40 mg/day in the Heart Protection Study (HPS) also demonstrated the greatest risk reduction in subjects with HDL-C <35 mg/dL.[61]

A randomized parallel-group study evaluated the comparative dose efficacy of atorvastatin (10-80 mg), simvastatin (10-40 mg), pravastatin (10-40 mg), lovastatin (20-80 mg) and fluvastatin (20-40 mg) in 534 hypercholesterolemic patients.[68] While atorvastatin was the most effective agent for lowering LDL-C, no significant differences in HDL-C effects were noted between atorvastatin and the other statins tested, except at the 40 mg dose when simvastatin produced greater increases than atorvastatin. The Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) study has recently extended these findings, demonstrating that rosuvastatin 10-40 mg was more efficacious for reducing levels of LDL-C and raising HDL-C compared with mg-equivalent doses of atorvastatin, simvastatin or pravastatin (all $P<0.001$).[69] After 6 weeks in this randomized study of 2431 adults with hypercholesterolemia, rosuvastatin 10-40 mg reduced mean LDL-C levels by 45.8-55.0%. Across dosage ranges, the HDL-C-increasing effect of rosuvastatin was consistent (in contrast to atorvastatin) and was significantly higher than that of simvastatin or pravastatin.

Therapy options available for patients whose HDL-C level remains low despite statin therapy include switching to a more efficacious statin. Data from the Measuring Effective Reductions in Cholesterol Using Rosuvastatin TherapY (MERCURY) I study showed that patients switched to rosuvastatin from a comparator statin had greater reductions in LDL-C and greater increases in HDL-C compared with those who remained on the comparator.[70] These comparative studies demonstrate differences between statins in their efficacy for lowering LDL-C and raising HDL-C and highlight the importance of selecting the most appropriate statin for maximizing improvements across the lipid profile.

Compositional changes in HDL are an important consideration with regards to atherosclerosis risk. A randomized crossover study of 86 hypercholesterolemic (LDL-C ≥130 mg/dL, triglycerides <400 mg/dL) CHD patients compared the effects of atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin on HDL subclass profiles[71] and demonstrated that the most effective agents for lowering LDL-C and triglyceride levels had the largest effect on increasing the anti-atherogenic α-1 HDL subclass.

Certain patients may require further modification of HDL-C levels with the addition of a second lipid-modifying

Table 3 Clinical effects related to HDL-C of statin therapy in placebo-controlled angiographic and clinical end point trials

Study	n	Patients	Lipid criteria	Statin	Follow up (years)	Main findings
Lipoprotein and Coronary Artherosclerosis Study[63,64]	339	Men and post-menopausal women; 35-75 years; angiographically determined coronary artery disease	LDL-C 115-190 mg/dL; 68 with HDL-C <35 mg/dL	Fluvastatin (40 mg/day)	2.5	Reduction vs placebo in angiographic lesion progression by HDL-C level: <35 mg/dL: 76.3% (P=0.0004) ≥35 mg/dL 56.6% (P=0.09) 2.5-year event rates by HDL-C level: <35 mg/dL: fluvastatin = 4.7%; placebo = 32% (P=0.002) ≥35 mg/dL: fluvastatin = 14.8%; placebo = 9.8% (P=0.232)
Air Force/Texas Coronary Atherosclerosis Prevention Study[65]	6605	Men 45-73 years; women 55-73 years; no clinical atherosclerosis	Average total cholesterol and LDL-C; low HDL-C levels (mean 36 mg/dL for men; 40 mg/dL for women)	Lovastatin (20-40 mg/day)	5.2	Increase in mean HDL-C level after 1 year: lovastatin = 6%; placebo = 1.2% (P<0.001) Risk reduction by HDL-C tertile: ≤34 mg/dL: 45% 35–39 mg/dL: 44% ≥40 mg/dL: 15%
Prospective Study of Pravastatin in the Elderly at Risk[66]	5804	Men and women; 70-82 years; history of or risk factors for cardiovascular disease	2051 with HDL-C <43 mg/dL	Pravastatin (40 mg/day)	3.2	Hazard ratios for primary end point (coronary death, non-fatal myocardial infarction, or fatal or non-fatal stroke) by HDL-C level vs placebo: <43 mg/dL: 0.64 43-53 mg/dL: 0.93 >53 mg/dL: 1.09 P=0.0069 for heterogeneity of treatment across subgroups
Heart Protection Study[61]	20 536	Men and women; 40-80 years; coronary artery disease, occlusive arterial disease, or diabetes	Mean HDL-C 41 mg/dL; 7176 with HDL-C <35 mg/dL	Simvastatin (40 mg/day)	5.0	Reduction vs placebo in rate of first major vascular event[a] by HDL-C level: <35 mg/dL: 24% 35-42.5 mg/dL: 20% ≥42.5 mg/dL: 19% χ^2 trend = 1.98

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

[a]Non-fatal myocardial infarction or cardiac death.

agent to treatment with an efficacious statin. Clinical trials have demonstrated a reduction in CHD events associated with fibrate therapy in patients with low HDL-C that was most often accompanied by high triglycerides (Table 4). The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) with gemfibrozil demonstrated that raising HDL-C in patients with established CHD and low HDL-C levels is at least partly responsible for a significant reduction in CHD risk. VA-HIT enrolled 2531 patients with CHD and low levels of HDL-C (≤40 mg/dL) and LDL-C (≤140 mg/dL).[73] Compared with placebo, treatment with gemfibrozil for 1 year increased HDL-C by 6% and decreased triglyceride levels by 31%, with no change in LDL-C levels. Moreover, patients receiving active treatment demonstrated a 22% reduction ($P=0.006$) in risk for the primary combined end point (non-fatal MI or death from CHD). Further analysis revealed a strong correlation between non-fatal myocardial infarction plus CHD death and on-treatment concentrations of HDL-C but not triglycerides or LDL-C.[74]

Of all available drugs, niacin provides the greatest increase in HDL-C levels, although its use may be limited by poor tolerability.[60] Nevertheless, niacin has been effectively used in combination with statin therapy. For example, a 3-year, double-blind study has been conducted in 160 CHD patients with low HDL-C (≤35 mg/dL in men, ≤40 mg/dL in women) and normal LDL-C levels, in which participants received simvastatin plus niacin, anti-oxidant therapy, simvastatin plus niacin and anti-oxidants, or placebo.[77] Simvastatin plus niacin reduced LDL-C levels by 42% and increased HDL-C levels by 26%. The combination regimen caused regression of proximal coronary stenosis and was associated with a 90% reduction in risk of the composite end point of coronary death, non-fatal MI, stroke or revascularization. It is worth noting, however, that no conclusions can be drawn regarding the additional benefit of combining niacin with a statin because statin monotherapy was not included as a treatment regimen. The Arterial Biology for the Investigation of the Treatment of Reducing Cholesterol (ARBITER) 2 study recently examined the effects of extended-release niacin (1000 mg daily) compared with placebo on carotid intima-media thickness in 167 patients with CHD and low HDL-C (<45 mg/dL) receiving statin monotherapy.[78] After 1 year, HDL-C increased significantly in the niacin group (21%, $P=0.002$) and was unchanged in the placebo group. In addition, mean carotid intima-media thickness increased significantly in the placebo group (0.044, $P<0.001$) and was unchanged in the niacin group (0.014 mm, $P=0.023$). Although the difference between these rates was not statistically significant ($P=0.08$), this trial provides further support for treatment of low HDL-C levels as a secondary target of dyslipidemia therapy.

Thiazolidinediones are a class of drugs used primarily to lower blood sugar levels by improving insulin resistance. These agents can increase HDL-C levels but may also change the distribution of small LDL particles to larger cholesterol-enriched LDL particles, thus modestly increasing LDL-C levels.[79] Studies suggest that different agents in this drug class have divergent lipid effects. For example, in a study of 100 patients with type 2 diabetes previously receiving troglitazone, switching to pioglitazone was associated with a decrease in triglyceride levels, while changing to rosiglitazone was associated with an increase.[80] Although levels of HDL-C increased in both groups, pioglitazone improved HDL-C to a greater extent than rosiglitazone in patients with HDL-C <35 mg/dL at baseline.

New advances in HDL-based therapies

Apolipoprotein A-I Milano is a variant of apolipoprotein A-I originally identified in a small group of individuals in Italy who showed no clinical signs of CHD despite having very low levels of HDL-C.[81] The lack of CHD in these patients appears to result from apolipoprotein A-I Milano being more effective at mobilizing tissue cholesterol.[82] In a recent double-blind study in 57 randomized patients with acute coronary syndrome, administration of a recombinant apolipoprotein A-I Milano/phospholipid complex caused significant regression of coronary atherosclerosis whereas placebo did not.[83] It is unclear whether the use of a recombinant form of apolipoprotein A-I rather than A-I Milano would have produced the same effect, but the findings imply that targeting HDL-C to reduce cardiovascular events is both reasonable and feasible.[3]

There has been controversy over the benefit of cholesteryl ester transfer protein inhibitors for raising HDL-C levels. Blocking the transfer of cholesteryl esters from HDL to LDL should increase the level of HDL-C and might therefore be expected to reduce cardiovascular risk. Indeed, a cholesteryl ester transfer protein inhibitor has been shown to attenuate atherosclerosis in rabbits.[84] However, in a study of Japanese American subjects with mutations in the cholesteryl ester transfer protein gene that resulted in reduced levels of the protein, elevated HDL-C levels were accompanied by an increase in cardiovascular risk.[85] Nevertheless, cholesteryl ester transfer protein inhibitors are now in clinical development and have demonstrated potential for increasing HDL-C. A randomized, placebo-controlled trial evaluated the efficacy and safety of daily treatment with JTT-705 in 198 healthy subjects with mild hyperlipidemia.[86] After 4 weeks' treatment with JTT-705 (300-900 mg/day), HDL-C was increased by 16-34%, and LDL-C was decreased by 7% in the 900 mg group. An increase in apolipoprotein A-I was also noted. The 900 mg/day dose was associated with a higher frequency of gastrointestinal complaints compared with placebo, although the difference was not statistically significant. More recently, clinical data with another inhibitor, torcetrapib, have been published. In a 2-week dose-ranging study of 8 healthy subjects with baseline HDL-C of 52 ± 12 mg/dL, torcetrapib (10-240 mg/dL) was accompanied by a 16 to 91% increase in HDL-C.[87] A single-blind, placebo-controlled study examined the effects of torcetrapib, alone and in combination with ator-

Table 4 Clinical effects related to HDL-C of fibrate therapy in placebo-controlled angiographic and clinical end point trials

Study	n	Patients	Lipid criteria	Fibrate	Follow up (years)	Main findings
Lopid Coronary Angiography Trial[72]	395	Men; ≤70 years; post-coronary artery bypass grafting	HDL-C ≤42.5 mg/dL; LDL-C ≤174 mg/dL; triglyceride ≤354 mg/dL	Gemfibrozi (1200 mg/day)	2.7	Change in HDL-C: 21 vs 7% with placebo ($P<0.001$) Progression of coronary atherosclerosis was attenuated relative to placebo (change in minimum luminal diameter of stenoses −0.04 vs −0.09, $P=0.002$)
Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial[73,74]	2531	Men; <74 years; CHD	HDL-C ≤40 mg/dL; LDL-C ≤140 mg/dL	Gemfibrozi (1200 mg/day)	5.1	Change in HDL-C at 1 year: 6% vs placebo ($P<0.001$) Risk reduction vs placebo: myocardial infarction or CHD death: 22% ($P=0.006$); non-fatal myocardial infarction: 23% ($P=0.02$) A change of 5.0 mg/dL in on-treatment HDL-C associated with an 11% decrease in rate of myocardial infarction or CHD death ($P=0.02$)
Helsinki Heart Study[75]	4081	Men; 40-55 years; no CHD	Non-HDL-C ≥200 mg/dL	Gemfibrozi (1200 mg/day)	5.0	Change in HDL-C over first 2 years: 11 vs −2% with placebo Risk reduction vs placebo: cardiac end points[a]: 34% ($P<0.05$); non-fatal myocardial infarction: 37% ($P<0.05$)
Bezafibrate Infarction Prevention Study[76]	3090	Men and women; 45-74 years; CHD	HDL-C ≤45 mg/dL; LDL-C ≤180 mg/dL; triglyceride ≤300 mg/dL	Bezafibrate (400 mg/day)	6.2	Change in HDL-C: 18 vs 4% with placebo Risk reduction vs placebo: myocardial infarction or sudden death: 9.4% ($P=0.26$); non-fatal myocardial infarction: 12.8% ($P=0.18$)

CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

[a]Includes myocardial infarction, sudden cardiac death and unwitnessed death.

vastatin, on plasma lipoprotein levels in 19 subjects with HDL-C levels <40 mg/dL.[88] Treatment with torcetrapib 120 mg/day as monotherapy increased HDL-C levels by 46% and by 61% when used in combination with atorvastatin 20 mg/day. Twice-daily treatment with torcetrapib 120 mg increased HDL-C levels by 106%. Additionally, torcetrapib reduced LDL-C levels both when given as monotherapy and in combination with atorvastatin. While these findings hold promise, further studies are needed to determine whether the increase in HDL-C with these agents translates into a reduction in CHD risk.

Conclusions

The link between LDL-C lowering and the prevention of CHD is well established. However, many patients remain at risk of CHD despite having LDL-C levels below recommended targets. It is clear that low levels of circulating HDL-C are also associated with increased risk of CHD, and this has heightened interest in the potential of this lipoprotein fraction as a secondary therapeutic target.

Lifestyle changes are recommended for the prevention of CHD, and these often have beneficial effects on lipid levels, including raising HDL-C levels. Statins are first-line drug therapy for treating dyslipidemia and their utility for preventing CHD events has been established. Statins can raise HDL-C levels, although their efficacy for improving this lipoprotein fraction varies. Adding a fibrate or niacin to statin therapy can provide further improvements in HDL-C. However, the putative benefit of combined therapy with a statin and niacin or fibrate versus statin monotherapy awaits confirmation in randomized clinical trials. Meanwhile, selecting a statin that is efficacious across the lipid profile, thereby maximizing the benefits of treatment on both LDL-C and HDL-C, may reduce the need for combination therapy. While lowering LDL-C remains the primary therapeutic goal, evidence suggests that raising low HDL-C as a secondary target of therapy will have additional benefits for CHD risk reduction.

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