FEATURED REVIEW ARTICLE

High-Density Lipoprotein Cholesterol Therapies

THE NEXT FRONTIER IN LIPID MANAGEMENT

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■ Current cholesterol treatment guidelines target low-density lipoprotein cholesterol as the primary goal of therapy and recommend statins as first line therapy. However, despite aggressive treatment and success at reaching the recommended goals, coronary heart disease is still a leading cause of morbidity and mortality. Thus, other lipoproteins, such as high-density lipoprotein, are now being looked to as the next promising targets of therapy to help reduce the burden of coronary heart disease and atherosclerosis. This review details currently available strategies to raise high-density lipoprotein cholesterol, and then turns to several new compounds in development that target the varying components of the complex metabolism of high-density lipoprotein.

KEY WORDS

apoA-I

cholesteryl ester transfer protein

fibrates

high-density lipoprotein cholesterol

niacin

peroxisome proliferator-activated receptor

reverse cholesterol transport

rimonabant

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INTRODUCTION

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines for cholesterol treatment target low-density cholesterol (LDL-C) as the primary goal of lipid therapy given the abundance of excellent clinical trial data for both primary and secondary prevention of adverse coronary events by lowering LDL-C.[1] In fact, even more aggressive goals for treatment of LDL-C are now recommended given recent clinical trial data[2]; however, despite treating to lower LDL-C targets, coronary heart

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disease (CHD) is still the leading cause of morbidity and mortality in the United States. Even patients who reach these aggressive LDL-C goals still experience a significant number of coronary events. Thus, increasing attention is being focused on other lipoprotein fractions as additional potential targets of therapy.

High-density lipoprotein cholesterol (HDL-C) represents a major target for reducing cardiovascular risk. Numerous prospective epidemiologic studies have demonstrated HDL-C levels to be inversely related to the risk of CHD.[3] There is also evidence from controlled clinical trials supporting the theory that treating patients who have low HDL-C with various lipid-lowering therapies, including statins, fibrates, and niacin, has the potential to reduce major coronary events.[4–9] The ATP III recognizes low HDL-C (<40 mg/dL) as a major risk factor for CHD, as well as the clustering of low HDL-C with other cardiac risk factors comprising the metabolic syndrome.[1] The ATP III treatment recommendations for low HDL-C include intensification of lifestyle therapy and consideration of nicotinic acid or fibrate therapy in addition to an LDL-lowering drug, especially in high-risk patients.[2] However, there is no target HDL-C level at this time due to lack of clinical outcome data to support such a goal.

Despite successes at reaching aggressive LDL-C goals and thereby reducing CVD risk, there is still a large, unmet need for further risk reduction. A logical next step is to expand our focus to the modification of other lipoprotein fractions such as HDL. However, in comparison to treatment of LDL-C, where moderate doses of medications such as statins can lead to 50% reductions in levels, therapies available to raise HDL-C generally only result in modest increases. Therefore, there is also a pressing need to develop new therapeutics that raise HDL-C levels and/or improve HDL-C function. This review will focus on several strategies already widely available for raising HDL-C and then briefly discuss therapies currently under clinical investigation that have promise for atherosclerosis reduction by targeting the mechanism of action and the metabolism of HDL.

CURRENT APPROACHES TO HDL-C MODIFICATION

Lifestyle Modification

First-line treatment to raise HDL-C is lifestyle modification, including diet, weight control, aerobic exercise, smoking cessation, and moderate alcohol consumption. ATP III guidelines recommend reducing intake of saturated fats to <7% of total calories and total fat to only 25% to 35% of total calories, mainly for the LDL-lowering effect.[1] Dietary fat effects on HDL are complex; diets high in saturated fats tend to increase HDL-C levels, and those abundant in monounsaturated fats tend to be HDL-C neutral.[10] A type of polyunsaturated fat, omega-3 fatty acids, have been gaining increased attention for their numerous reported cardiovascular benefits and deserve mention here. Prospective epidemiologic studies in various populations, as well as several case-control studies, suggest that patients who consume fish and have diets high in omega-3 fatty acids (ie, EPA and DHA) may have lower CHD mortality and decreased incidence of sudden cardiac death.[11] In addition, in randomized controlled trials, omega-3 fatty acids have been shown to reduce overall mortality, reduce the risk in secondary CHD prevention, and even reduce angiographic progression of atherosclerotic plaque.[11] The mechanisms of the risk reductions are still unclear; however, the main lipoprotein benefit seems to be reduction in triglycerides. Although only small HDL-C elevations are seen with omega-3 fatty acids and such supplements should not be prescribed for their HDL effect, this type of fat should be present in adequate amounts in all "heart-healthy" diets and saturated fats should be kept to a minimum.

In the Framingham Offspring Study, there is a clear inverse correlation between obesity and both HDL-C and apolipoprotein A-I (apoA-I) levels.[12] Low HDL-C levels are also associated with increased waist circumference and the metabolic syndrome. The effect of weight loss on HDL-C levels has been evaluated in many trials over the years, with the main effect being a small increase in HDL-C levels once weight stabilizes at the new, lower level.[13] One meta-analysis determined that HDL-C levels increase by 0.35 mg/dL per kilogram of weight loss.[14] A reasonable approach to weight reduction is a gradual loss by both dietary means and exercise to achieve a body mass index in the "normal" range of 18.5 to 25.

Aerobic exercise can lead to a modest increase in HDL-C, especially in patients who have the combination of low HDL-C and high triglycerides; unfortunately, exercise does not seem to increase HDL-C levels in those patients with isolated low HDL-C.[15] Overall, the HDL effect with exercise training seen in many studies is surprisingly small, at only 1 to 2 mg/dL increases.[16] However, there are multiple other cardiovascular benefits of regular aerobic exercise, which makes it a part of a comprehensive lifestyle intervention program.

Cigarette smoking depresses HDL-C levels, especially in women,[17] and smoking cessation can significantly increase HDL-C levels.[18] In one meta-analysis, there was a 3.85 mg/dL increase in HDL-C following smoking cessation.[18] Smoking cessation is always advised for overall cardiovascular risk reduction. Conversely, moderate alcohol consumption, defined as 1 drink per day for women or 1 to 2 drinks per day for men, has been shown to correlate with higher HDL-C levels.[17,19] Moderate alcohol consumption is generally not recommended but is

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reasonable for those who chose to do so and have no contraindications.

Pharmacologic Therapy

Statins

Most high-risk patients with low HDL-C should probably be prescribed statin therapy as first-line lipid management. The main effect of statins is to lower LDL-C by inhibiting 3-hydroxy-3-methyglutaryl-coenzyme A reductase, which interferes with cholesterol biosynthesis. In addition, the average statin will raise HDL-C by 5% to 10%.[1] The mechanism of these increases is likely multifactorial and is possibly partially related to reduced cholesteryl ester transfer protein (CETP) and increased transcription of the apoA-I gene.[20,21] Due to their weak HDL-C effects, statins should continue to be used primarily for their potent LDL-C–lowering effects.

Niacin

In addition to lifestyle modification, it is also reasonable to consider adding pharmacologic therapy in high-risk patients who have reached their LDL-C goal. Currently, niacin is the most potent HDL-C–raising agent available. Niacin therapy can result in a 15% to 35% dose-dependent increase in HDL-C[1]; however, use of niacin is occasionally limited by the main side effect of flushing. Niacin can also lower LDL-C by 5% to 25% and triglycerides by 20% to 50%.[1] The exact HDL-raising mechanism of niacin has not yet been fully elucidated and is likely multifactorial.[22] Recently, the receptor for niacin was discovered,[23] which should help further elucidate the mechanism of action as well as provide a new target for pharmacologic therapy.

Despite its unclear mechanism, niacin therapy has been shown to reduce clinical CHD events. In the Coronary Drug Project, patients with prior myocardial infarction who were treated with niacin for 5 years had a significant reduction in mortality and in myocardial infarction.[9] Studies looking at niacin in combination with other agents such as statins and fibrates have also demonstrated that niacin is both safe and effective. In the placebo-controlled HDL Atherosclerosis Treatment Study (HATS), long-acting niacin in combination with simvastatin proved to be safe as well as effective in reducing both clinical events and in slowing angiographic progression of coronary disease in patients with CHD and low HDL-C.[24,25] The more recent ARBITER 2 trial examined the addition of once-daily extended-release niacin versus placebo to baseline statin therapy, also in patients with known CHD and low levels of HDL-C.[26] In this double-blind, randomized trial, after 1 year of treatment, there was no change in carotid intima-media thickness in the niacin group; however, patients in the statin-only group had significant progression.[26] Adherence was excellent despite a high incidence of flushing in the niacin group.[26]

Niacin in combination with fibrates has also been proven to reduce cardiovascular mortality[27] and is generally considered safe. A recent trial examined the sequential addition of gemfibrozil plus niacin plus cholestyramine compared to placebo on angiographic progression of CHD and occurrence of clinical events in patients with established CHD and low HDL-C.[28] Overall, the treatment group had a 36% increase in HDL-C levels as well as a significant difference from the placebo group in focal coronary stenoses.[28] Additionally, there was a trend to a risk reduction for a composite clinical cardiovascular end point; however, the difference did not reach statistical significance.[28] There were no major adverse events in this trial.

Given the safety of niacin in combination with multiple other lipid-modifying therapies, it is a reasonable approach to add niacin to concurrent lipid therapy in high-risk patients with low HDL-C once the target LDL-C and triglyceride levels have been achieved. In order to minimize the side effect of flushing, initiation of niacin should start with a low dose of the extended-release formulation with gradual up-titration to the maximum of 2 g/d as tolerated.

Fibric Acid Derivatives (Fibrates)

Fibrates raise HDL-C by 5% to 20%[1] and work by agonizing peroxisome proliferator-activated receptor (PPAR)-α, which leads to increased synthesis of apoA-I, the main HDL-associated apolipoprotein, thereby enhancing the formation of new HDL particles.[29] Several randomized controlled trials with fibrates have demonstrated both primary and secondary prevention of cardiovascular events. In the Helsinki Heart Study, a primary prevention trial of gemfibrozil in dyslipidemic middle-aged men, there was a significant reduction in major CHD events, especially in the subgroup of patients with elevated triglycerides.[8] Similar subgroup analysis was seen in the Bezafibrate Infarction Prevention Study.[7] The secondary prevention, Veterans Affairs HDL Intervention Trial, showed a significant 22% reduction in events, with a modest 6% increase in HDL-C in patients with low HDL-C and CHD after treatment with gemfibrozil for approximately 5 years.[6] Multivariate analysis determined that CHD events were reduced by 11% for every 5 mg/dL increase in HDL-C; however, the change in HDL-C only partially explained the benefit of gemfibrozil with regard to reduction in clinical CHD events.[30] Given current clinical evidence, it is prudent to prescribe fibrate therapy for those patients with both low HDL-C and elevated triglycerides, again, once the LDL-C goal is met.

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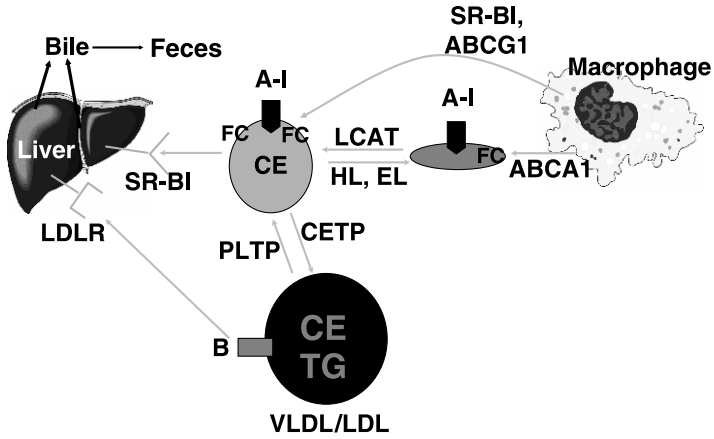

Figure 1. A schematic diagram of HDL metabolism and reverse cholesterol transport. Cholesterol efflux out of macrophages can occur by several mechanisms. In the best-established pathway, lipid-poor apoA-1 (A-1) acquires free cholesterol (FC) from macrophages through an efflux process mediated by adenosine triphosphate-binding cassette protein A1 (ABCA1) to form pre-β-HDL. FC is then converted to cholesteryl esters (CE) by lecithin-cholesterol acyltransferase (LCAT) to form mature HDL-C. CEs in mature HDL can then be returned to the liver for excretion. Alternatively, CEs can be transferred to the apoB-containing lipoproteins (VLDL/LDL) by the action of CETP to be returned to the liver via the low-density lipoprotein receptor (LDLR). Other components include adenosine triphosphate-binding cassette protein G1 (ABCG1), scavenger receptor class B1 (SR-B1), hepatic lipase (HL), endothelial lipase (EL), and phospholipids transfer protein (PLTP).

Thiazolidinediones

The thiazolidinediones, which are agonists of PPAR-γ, also have a modest HDL-C-raising effect when studied in diabetics, with an average elevation of around 5% to 15%.[31] Results from forthcoming clinical trials also look promising for the benefit of these medications in reducing vascular events. The recently published PROactive trial, a 3-year prospective, randomized, double-blind, placebo-controlled trial of pioglitazone in type 2 diabetics with a history of macrovascular disease, showed a significant 16% reduction in the combined secondary end point of all-cause mortality, nonfatal myocardial infarction, and stroke.[32] The primary composite end point in this study, the above end points plus amputation, leg revascularization, coronary revascularization (including CABG or PTCA), or acute coronary syndrome, was 10% lower in the pioglitazone group, although this risk reduction did not reach statistical significance.[32] Although these results are exciting, the HDL-C effect of thiazolidinediones on HDL-C is still only modest, and these medications are only indicated for type 2 diabetics. Before thiazolidinediones can be used more widely for vascular protection, such as in high-risk patients with low HDL-C and the metabolic syndrome, clinical outcome trials must be performed in these populations.

HDL METABOLISM AS A TARGET FOR NEW DRUG THERAPIES

The exact atheroprotective mechanisms of HDL are multifactorial and not yet fully understood. The most popular theory of atheroprotection is that of reverse cholesterol transport (RCT), in which excess cholesterol is removed from the macrophage by HDL and returned to the liver for excretion (Figure 1).[33] Other properties of HDL have also been described, including anti-oxidative and anti-inflammatory properties, vascular and endothelial protective effects, and antithrombotic activity,[34–36] all of which could, in theory, contribute to increased vascular protection and reductions in clinical events.

An important and emerging concept in HDL metabolism and therapeutics is that simply raising HDL-C levels may not be the optimal target for new HDL therapies. One theory is that the function of HDL may be more important than the plasma concentration[37] and that therapies which improve HDL function could have significant anti-atherogenic and vascular protective effects without increasing HDL-C levels. Thus, in order to measure "HDL function" advances in the field of HDL, functional markers must take place simultaneously.

Given the varied mechanisms of HDL action, targeting HDL for therapeutic intervention is complex. From directly targeting apoA-I production and levels, to promoting cholesterol efflux out of macrophages, to slowing the removal of plasma HDL and apoA-I, there are varied approaches, all of which are new frontiers in lipid-modifying therapeutics. The following section explores several of the HDL-directed therapies currently under clinical investigation.

ApoA-I Infusions and Mimetics

Based on epidemiologic studies, we know that apoA-I levels are an independent and inverse risk factor for CHD, and it has been suggested that apoA-I levels

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correlate even more strongly with cardiovascular risk than do HDL-C levels.[38] ApoA-I acts in the first step of RCT, facilitating efflux of free cholesterol from macrophages via the adenoside triphosphate-binding cassette (ABC) A1 transporter pathway to form pre-β-HDL (Figure 1),[39] and is also postulated to have both antioxidative and anti-inflammatory effects. Given these pivotal roles of apoA-I, it has become a major target for new drug therapies. Studies performed in animals over the past decades consistently demonstrate that increases in apoA-I, even without elevations in HDL-C, lead to substantial reductions in the progression of atherosclerotic plaque.[40–42]

Early studies in humans confirmed that increases in apoA-I levels could be achieved by giving bolus infusions and that such infusions led to only minor increases in HDL-C levels.[43] Although wild-type apoA-I was never further developed to test the effect on atherosclerosis, there has been exploration of apoA-I Milano as a therapeutic. ApoA-I Milano is a rare gain-of-function point mutation in apoA-I that was described almost 30 years ago,[44] which is thought to result in increased anti-atherogenic effects.[45] Recently, a small, double-blind, placebo-controlled trial of the apoA-I Milano/phospholipids complex in patients with acute coronary syndrome was performed, which generated much excitement. After 5 weekly infusions of the complex, there was a significant 4.2% absolute reduction from baseline in atheroma volume as measured by intravascular ultrasound.[46] Conversely, the placebo group had a nonsignificant increase in atheroma volume.[46] There are several caveats regarding the future development of the apoA-I Milano compound.[47]

Another approach targeting apoA-I is to biochemically "mimic" the structure. Such apoA-I mimetic peptides have been developed in both injectible and oral forms and, indeed, have been shown to have similar properties to apoA-I, particularly in their ability to promote cellular cholesterol efflux.[48] One oral apoA-I mimetic peptide, D-4F, has been shown to dramatically reduce atherosclerosis in mice and rabbits without increases in HDL-C levels.[40,49] ApoA-I mimetics, which seem to act by promoting RCT as well as by reducing oxidized lipids without increasing HDL-C levels,[40] are an exciting therapeutic prospect that awaits further investigation.

New PPAR Agonists

As noted above, fibrates have been shown to reduce cardiovascular events and to raise HDL-C by acting as weak agonists of PPAR-α. This activation leads to downstream expression of apoA-I as well as to other pleiotropic effects, mainly anti-inflammatory effects.[29] Given these beneficial effects, it will be interesting to see if development of significantly more potent PPAR-α agonists will have additional HDL-raising or anti-atherogenic effects.

PPAR-γ, the target for TZDs, is also thought to promote cholesterol efflux.[50] As activation of both the PPAR-α and PPAR-γ nuclear receptors could be potentially anti-atherogenic as well as have complimentary lipid and metabolic effects, there has been interest in developing dual PPAR agonists. Currently, therapy with dual PPAR agonists is being tested for use in type 2 diabetics with atherogenic dyslipidemia. One such agent was recently presented to the FDA for approval, although an independent analysis of this data raised concerns regarding a potential increased incidence of a combined cardiovascular outcome with this medication.[51] Thus, the future of such medications is uncertain at this time and will require further investigation.

CETP Inhibitors

Cholesteryl ester transfer protein is a plasma glycoprotein that promotes the transfer of cholesteryl esters from HDL-C to apoB-containing lipoproteins, resulting in equilibrium between lipoprotein fractions (Figure 1).[52] The actual relationship between CETP level and CHD risk in humans is uncertain. CETP deficiency seems to be associated with elevated levels of HDL-C and apoA-I,[53] and a recent prospective epidemiologic study confirms an overall increased risk with increasing CETP quintiles (and correspondingly lower levels of HDL-C).[54] Regardless of this still uncertain relationship, 2 small molecule inhibitors of CETP are in clinical development.

The first CETP inhibitor to be studied in humans, JTT-705, has been tested for efficacy and safety in healthy, mildly dyslipidemic subjects.[55] In this study, treatment with the highest dose of JTT-705 (900 mg) for 4 weeks led to a significant 37% decrease in CETP activity and a 34% increase in HDL-C.[55] JTT-705 was well tolerated with only mild gastrointestinal side effects.[55] Subsequently, the effectiveness of JTT-705, in combination with statin therapy, was evaluated, a practical approach given that most patients with low HDL-C will be initially treated to their LDL-C goal with statin therapy. This trial showed that 600 mg of JTT-705 in combination with pravastatin 40 mg for 4 weeks in a similar dyslipidemic population resulted in significant increases in apoA-I and a significant 28% increase in HDL-C levels.[56]

Another CETP inhibitor, torcetrapib, has also been evaluated as monotherapy and in combination with statins. In a phase 1 multidose study of torcetrapib in healthy volunteers, impressive increases in HDL-C were seen, with up to 91% increase in HDL-C at the maximal dose of 120 mg twice daily.[57] In another small trial, torcetrapib was evaluated in a crossover study in patients with low HDL-C (<40 mg/dL), and a subset of which was also treated with atorvastatin.[58] Here, there

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were again impressive increases in HDL concentrations by 46% with torcetrapib 120 mg daily and by 61% in the combination treatment group.[58] Larger trials with actual and surrogate clinical cardiovascular end points are underway.

Rimonabant

An exciting new therapy with reported effects on many cardiovascular risk factors, including obesity, tobacco abuse, and dyslipidemia, that is pending FDA approval is rimonabant. Rimonabant blocks the cannabinoid-1 receptor (CB1), which is present in multiple tissues, including brain and adipose.[59] Preclinical trials supported a role for this receptor in the regulation of peripheral energy balance and body weight, and studies in animals demonstrated that blockade of CB1 resulted in a lean phenotype with resistance to diet-induced obesity and dyslipidemia.[59] The recently published RIO-Europe study evaluated the treatment of overweight and obese patients, some of whom also had hypertension or dyslipidemia, with 1 year of treatment with rimonabant versus placebo.[60] All components of the metabolic syndrome showed significant improvement in the treated group, including HDL-C, which increased significantly by about 10% even after adjusting for weight loss.[60] The safety profile was favorable. The effects of longer-term treatment remain to be seen, as well as exactly what therapeutic niche rimonabant will fill.

SUMMARY AND RECOMMENDATIONS

Despite aggressive LDL lipid management, CHD is still a major cause of morbidity and mortality. Targeting HDL could help reduce the burden of atherosclerosis and CHD, especially given the clear correlation between both low HDL-C and apoA-I levels and increased risk for CHD. A general approach to treatment of low HDL-C should include regular aerobic exercise, weight reduction, smoking cessation, a diet limited in carbohydrates but rich in omega-3 fatty acids, and, in many cases, statin therapy. Currently, our most potent HDL-raising drug therapy is niacin, which is reasonable to add in high-risk patients with low HDL-C. Additionally, fibrates should be considered for patients with low HDL-C and elevated triglycerides. On the horizon are novel therapies that target the complexities of HDL metabolism and RCT, such as directly administering apoA-I or apoA-I mimetics, using various nuclear receptor activators to promote cholesterol efflux out of macrophages, or using inhibiting compounds to slow the removal of plasma HDL and apoA-I. With each therapy that is developed, not only are we exploring mechanisms of reducing atherosclerosis, we are also learning more about the molecular mechanisms of HDL and RCT, which can then lead to the development of even more targeted therapeutics. The field of HDL therapies is entering an exciting time, one in which the next few decades will undoubtedly witness the addition of several HDL-modifying therapies to our armamentarium of agents designed to prevent and treat atherosclerosis.

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