

The Role of High-Density Lipoprotein Cholesterol in Atherothrombosis

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Abstract

Despite considerable progress in the development of new therapies to control atherosclerosis and its complications, coronary heart disease (CHD) remains the number one cause of death in the Western world. While low high-density lipoprotein (HDL) has been associated with increased risk for CHD, raising HDL to reduce risk of disease has yet to be accepted as a standard therapeutic strategy. Currently available drugs that raise HDL (e.g., nicotinic acid, fibric acid derivatives, peroxisome proliferator-activated receptor agonists, and statins) also affect low-density lipoprotein (LDL) and other lipid constituents, making independent interpretation of their HDL-raising effect difficult to tease apart. Nevertheless, basic science studies suggest that HDL has multiple beneficial effects, and current efforts to develop new pharmacologic products with potent HDL-elevating effects may herald a day when HDL elevation becomes part of standard management of atherosclerotic diseases.

Key Words: High-density lipoprotein cholesterol, atherosclerosis, coronary heart disease, HDL elevating therapy, dyslipidemia, nicotinic acid, fibrate, statin, cholesterol ester transfer protein inhibitor, peroxisome proliferator-activated receptor ligands.

Introduction

THE PAST HALF-CENTURY has seen tremendous progress in the fight against coronary heart disease (CHD). Modern medical therapy has resulted in a nearly 70% decrease in CHD-related deaths since 1950 (Fig. 1; 1). Yet despite this achievement, CHD remains the number one killer of Americans, with 1 in 5 Americans succumbing to this disease (2). With the aging of the American population, the socioeconomic impact of CHD will probably increase. While aging itself cannot be prevented, a lifestyle of healthy diet and exercise, and avoidance of tobacco products, can reduce one's risk level for the disease; appropriate pharmacologic

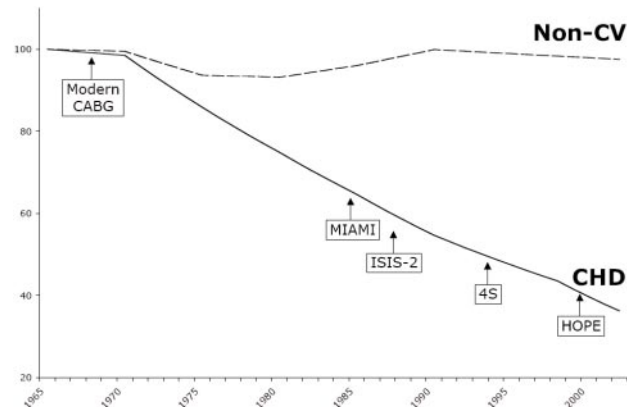


Fig. 1. Age-adjusted death rates in the United States secondary to coronary heart disease (CHD) and non-cardiovascular causes (Non-CV) by year, standardized to death rate in 1965 = 100 (1). This graph highlights some key clinical trials that may have played a role in the decline of CHD-related deaths, and future innovation will be needed to continue this progress.

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CABG: coronary artery bypass graft; MIAMI: Metoprolol in Acute Myocardial Infarction; ISIS-2: Second International Study of Infarct Survival; 4S: Scandinavian Simvastatin Survival Study; HOPE: Heart Outcomes Prevention Evaluation.

therapy can also help. For example, cholesterol-lowering statins decrease cardiovascular events by 20–40%; they have become a routine part of CHD management. Fewer than half of all patients with

Glossary

ACS = acute coronary syndrome
 apoA-I = apolipoprotein A-I
 CETP = cholesterol ester transfer protein
 CHD = coronary heart disease
 CIMT = carotid intima-media thickness
 DGAT2 = diacylglycerol acyltransferase 2
 DM = diabetes mellitus
 ETC-216 = apoA-I Milano
 HDL = high-density lipoprotein
 HPETE = hydroperoxyeicosatetraenoic acid
 HPODE = hydroperoxyoctadecadienoic acid
 HRT = hormone replacement therapy
 IDL = intermediate-density lipoprotein
 IVUS = intravascular ultrasound

LDL = low-density lipoprotein
 LDLr = LDL receptors
 LRP_r = LDL-related protein receptors
 PGI₂ = prostacyclin
 PON = paraoxonase
 PPAR- α = peroxisome proliferator-activated receptor- α
 RCT = reverse cholesterol transport
 SERM = selective estrogen receptor modulator
 TFPI = tissue factor pathway inhibitor
 TG = triglycerides
 TIA = transient ischemic attack
 TNF = tumor necrosis factor
 TZD = thiazolidinedione
 VLDL = very-low-density lipoprotein

symptomatic CHD were receiving lipid-lowering therapy in 2001 (2), but less than three years later, a national registry of patients admitted for CHD-related problems revealed that 88% received a cholesterol-lowering agent as one of their discharge medications (3). With all this progress, it remains somewhat frustrating that CHD is still the number one cause of death; therefore, considerable research is being undertaken to develop new pharmacologic strategies to further combat this epidemic. While statins have become a mainstay of modern CHD therapy, they primarily address one component of the lipid profile: low-density lipoprotein (LDL), the “bad cholesterol.” As LDL is aggressively lowered, progression of atherosclerosis slows and patients with CHD have fewer deaths and heart attacks (4, 5). If LDL levels are optimized by aggressive use of statins, additional lowering may not result in meaningful additional benefit; therefore, raising high-density lipoprotein (HDL) has attracted attention as a potential therapeutic adjunct to statin therapy.

HDL is popularly known as the “good cholesterol.” Population studies have demonstrated that as HDL levels increase, the incidence of CHD decreases. An analysis of four epidemiologic studies conducted in the United States suggested a 2–3% decrease in CHD risk for each 1% increase in HDL (6). The inverse relationship between HDL and CHD invites speculation that raising HDL may be an ideal therapeutic goal, to help decrease CHD. Furthermore, low HDL levels are very common among Americans, and 26.4% of those over 20 years old (39% of men and 15% of women) have low HDL (defined as HDL less than 40 mg/dL) (2, 7). Guidelines adopted by the American Heart Association, however, stop short of recommending HDL elevation as a specific therapeutic goal, pri-

marily for three reasons (8). First, correlation does not imply causation; low HDL level and CHD may be related, but some other factor that affects both HDL and CHD may be the true culprit. Second, currently available therapies that have an HDL-raising effect also affect atherogenic lipoproteins such as LDL, so the effect that can be attributed solely to the HDL increase is difficult to tease out (Table 1; 8–10). Third, lifestyle changes such as taking up exercise and quitting smoking also raise HDL, and these interventions come without pharmacologic side effects. Nonetheless, with 20% of American deaths from CHD, new interventions are necessary, and research continues to accumulate supporting HDL elevation as a potential target. In this review, we explore the rationale behind this strategy.

The Role of HDL in Lipid Metabolism

Cholesterol in the body is composed chiefly of LDL (“bad”) and HDL (“good”). LDL deposits lipids in the arterial wall, making the artery narrower, but HDL transports the lipids back to the liver. This balance between LDL and HDL is critical to the rate of formation of atherosclerotic lesions. If the proportion of LDL to HDL is raised, then more lipids will be deposited in arterial walls, leading to greater CHD, but if the ratio of HDL to LDL is elevated, then atherosclerotic lesions may regress, contributing to a reduction in heart attacks (Fig. 2).

Understanding this balance between LDL and HDL allows one to see the promise of HDL-elevating therapy. Designing therapeutic strategies, however, requires a greater understanding of how **reverse cholesterol transport** works. HDL plays a central role in lipoprotein metabolism (Fig. 3). The

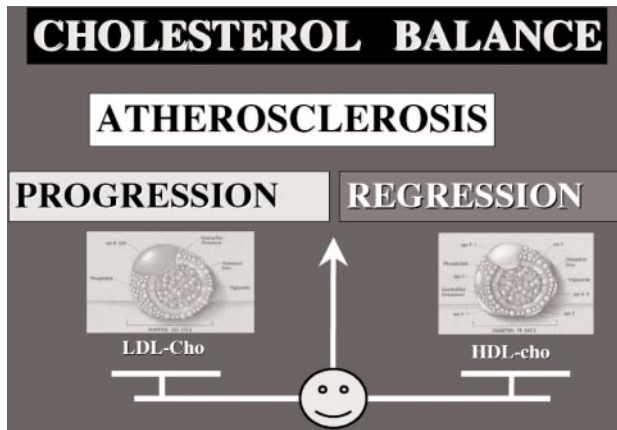


Fig. 2. The balance of LDL to HDL tips the scale toward atherosclerotic progression if there is more LDL or toward regression if there is more HDL.

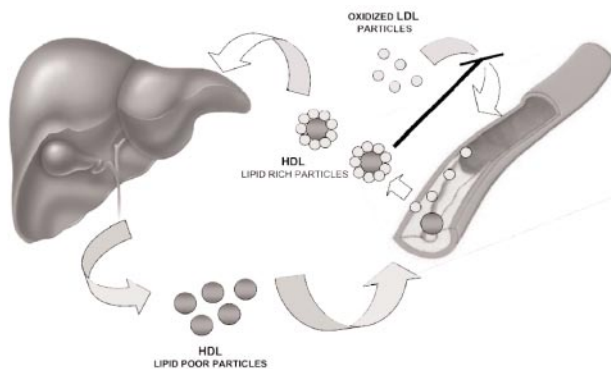


Fig. 3. The role of HDL in lipoprotein metabolism. HDL may prevent atherosclerotic development by engaging in reverse cholesterol transport from the arterial wall to the liver as well as blocking oxidized LDL particles from accumulating in the artery.

liver secretes apolipoprotein A-I (apoA-I), which acts like an empty vessel to accumulate lipids. Once the apoA-I has absorbed lipids from the arterial wall, it becomes HDL. HDL may accept additional free cholesterol from the vessel wall via another pathway on vessel wall macrophages (11). The lipid-laden HDL may then transport the removed cholesterol to the liver for disposal. This process, termed “reverse cholesterol transport” (RCT), is the principal mechanism behind the hypothesized benefit of HDL elevation. Much recent attention has focused upon a second HDL-based RCT mechanism. Cholesterol within HDL is transferred to LDL by a protein called “cholesterol ester transfer protein” (CETP), and this LDL may be returned to the liver by LDL receptors (LDLr) and LDL-related protein receptors (LRPr) (12). HDL also prevents arterial wall macrophages from absorbing oxidized LDL by hydrolyzing it (13). The

final mechanism by which HDL may prevent atherosclerosis is by decreasing the number of endothelial cell adhesion molecules, which serve as an entry point for monocytes into the arterial wall (14).

Understanding the biology of HDL allows us to speculate upon the effects of potential therapeutic targets on its metabolic pathway. Increasing apoA-I or decreasing CETP, for example, would probably increase the quantity of HDL; however, RCT may not necessarily increase in both situations—if the elevation in HDL is limited to lipid-laden HDL without hepatic uptake, then HDL elevation alone may falsely indicate clinical benefit. If HDL elevation, however, successfully results in reduction in lipid content within the vascular wall, then the atherosclerotic lesion may resemble a more stable plaque that is lipid-poor and with a thicker fibrous cap rather than a lipid-rich plaque with a thin fibrous cap, which is more vulnerable to rupture that can cause myocardial infarctions (15).

Other Protective Effects of HDL

HDL has other effects beyond RCT that reduce atherosclerosis. The antioxidant, anti-inflammatory, endothelial function enhancement, and antithrombotic properties of HDL suggest a beneficial effect independent of RCT (Fig. 4).

Antioxidant Effects

Oxidized LDL attracts monocytes, and when monocytes consume oxidized LDL, they become foam cells. Foam cells cause platelets to become more active, smooth muscle cells to proliferate and thicken the arterial wall, and arteries to constrict by decreasing nitric oxide, a potent vasodilator (16). As an antioxidant, HDL can inhibit the oxidation of LDL, thereby preventing these steps

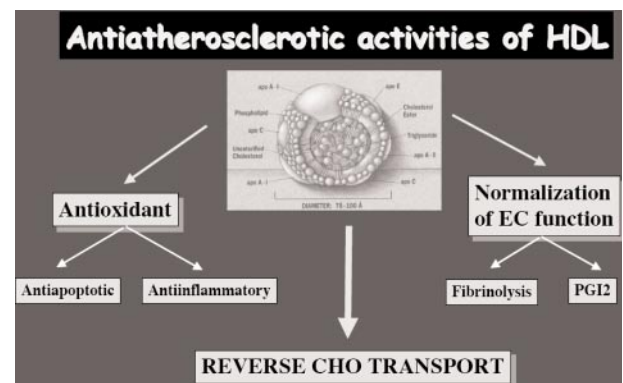


Fig. 4. Atheroprotective features of HDL include effects beyond reverse cholesterol transport.

from occurring. The reason for HDL's antioxidant effect may simply be its high antioxidant content, but HDL also contains several enzymes which directly prevent LDL oxidation. HDL transports an enzyme called paraoxonase (PON), which catalyzes the degradation of oxidized LDL phospholipids (17). If these oxidized phospholipids were not degraded, they could stimulate an inflammatory response and subsequent monocyte adhesion to the endothelium, accelerating atherosclerosis (18). The importance of PON's antioxidant effect has been further demonstrated in animal studies. In the absence of PON activity, HDL loses its atheroprotective effect in a mouse model (19), but increased expression of apoA-I increases PON activity (20). Furthermore, genetically modified animals that do not have PON are more susceptible to atherosclerosis (21), but those that overexpress PON have less atherosclerosis (22). Population studies of humans confirm the benefit of PON. Patients with more PON have fewer heart attacks (23), and low PON activity in a cohort of adult men was associated with more heart attacks (24). ApoA-I itself may also exert an anti-oxidant effect by reducing the "seeding molecules" hydroperoxyeicosatetraenoic acid (HPETE) and hydroperoxyoctadecadienoic acid (HPODE), which induce the oxidation of lipoprotein phospholipids (25).

Anti-inflammatory Effects

Experimental evidence suggests that HDL may be directly anti-inflammatory. HDL inhibits an enzyme called sphingosine kinase in endothelial cells; this action decreases sphingosine 1-phosphate, a key molecule in mediating inflammatory processes also mediated by tumor necrosis factor (TNF) (26). In a pig model, HDL inhibited expression of IL-1 α -induced E-selectin, another marker of inflammation, by endothelial cells *in vivo* and *ex vivo*, further suggesting anti-inflammatory benefit (27).

Endothelial Function

Atherogenesis starts with a dysfunctional endothelium (28). Endothelial dysfunction initiates a cascade of events leading to blood that more easily clots, loss of nitric oxide, which causes blood vessels to constrict, and leukocyte adhesion and migration, which accelerates atherosclerotic plaque formation (Fig. 5; 29); but HDL improves endothelial function. Endothelial cells exposed to HDL decrease adhesion molecule expression, which prevents macrophage accumulation within the arterial wall (30). Also, in hypercholesterolemic men with endothelial dysfunction and

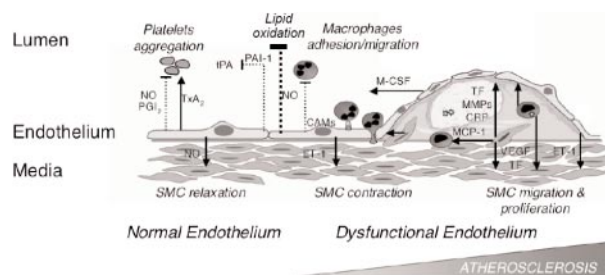


Fig. 5. Endothelial dysfunction initiates atherogenesis. Dysfunctional endothelium facilitates atherosclerosis development via impaired endothelium-dependent vasodilation, upregulated platelet aggregation and thrombogenicity, increased macrophage adhesion and migration and SMC proliferation (29).

CAM: cell adhesion molecule; CRP: C-reactive protein; ET: endothelin; MCP: monocyte chemotactic protein; M-CSF: monocyte colony stimulating factor; MMP: matrix metalloproteinase; NO: nitric oxide; PAI: plasminogen activator inhibitor; PGI₂: prostacyclin; SMC: smooth muscle cell; TF: tissue factor; tPA: tissue type plasminogen activator; TxA₂: thromboxane A₂; VEGF: vascular endothelial growth factor.

low HDL, infusion of HDL restored endothelial function by restoring NO bioavailability (31, 32). Also, HDL may exert an anti-apoptotic effect upon vascular endothelial cells, which prevents these cells from self-destructing (33). The prevention of apoptosis may make a plaque less vulnerable to rupture. Therefore, HDL may help across the spectrum of atherosclerotic disease by preventing initiation of atherogenesis by improving endothelial function, and additionally decreasing atherosclerotic burden and increasing plaque stability for patients with advanced disease.

Anti-thrombotic Effects

When atherosclerotic plaques rupture, thrombus formation occurs—it is this thrombus that can have devastating consequences if it completely occludes the vessel. Experimental evidence suggests that HDL is also anti-thrombotic, which may help to prevent this type of vessel closure, and the myocardial infarctions that result. In a study of hypercholesterolemic men, serum HDL level was a significant independent predictor of platelet thrombus formation within the Badimon perfusion chamber (34). Also, addition of apoA-I inhibited arterial thrombus formation in a mouse model (35). In an *in vitro* study, HDL enhanced inactivation of coagulation factor Va, thereby reducing thrombogenicity (36). In another *in vitro* model, the protein components of HDL, specifically apoA-I and apoA-II, were found to activate fibrinolysis, which is the process by which thrombi are broken down (37). HDL would, therefore, shift the hemostatic bal-

ance to fibrinolysis over thrombosis, which is favorable to the patient vulnerable to acute coronary syndrome (ACS). Tissue factor potently increases thrombogenicity, and HDL also has been shown to contain a tissue factor pathway inhibitor (TFPI) (38). HDL and apoA-I have also been shown to decrease the procoagulant activity of red blood cells (39). Oxidized LDL is particularly thrombogenic (40), and by reducing LDL, HDL would be additionally anti-thrombotic. HDL also stabilizes prostacyclin (PGI₂), which prevents thrombus formation between platelets and the vessel wall (41). Therefore, the current evidence suggests an overall anti-thrombotic effect of HDL.

Pre-clinical Evidence for the Effects of HDL Elevation

Teasing apart the effects of HDL in clinical trials has been difficult, as the medications used to study the effect of HDL elevation affect the parameters of other lipids as well (e.g., LDL, triglycerides [TG], etc.). The direct effect of HDL, however, has been demonstrated in animal models. In the seminal work on HDL infusion by Badimon et al. (42), HDL infusion into rabbits fed with a high-cholesterol diet resulted in decreased progression and regression of established atherosclerotic lesions and aortic lipid content. In another study, plaque regression, as measured by intravascular ultrasound (IVUS), was seen after direct infusion of apoA-I Milano into hypercholesterolemic rabbits within 72 hours, suggesting that reverse cholesterol transport is extremely rapid with this drug (43). Interestingly, apoA-I Milano infusion was also shown to reduce in-stent restenosis in a pig coronary artery model, suggesting that the effect of apoA-I Milano may extend beyond just RCT and include reduction of this complication of stent placement (44).

Current Treatment Options for HDL Elevation

Table 1 lists cardiovascular drugs that are known to raise HDL. However, their multiple effects upon other lipid parameters, as mentioned above, limit our ability to understand their effect on HDL independent of their effect on LDL and TG.

Niacin

Niacin is a B complex vitamin used for the treatment of high cholesterol since the 1950s. Niacin makes apoA-I last longer in the body, facilitating greater RCT by making apoA-I more available (45). Niacin also inhibits an enzyme, hepatic diacylglycerol acyltransferase 2 (DGAT2), which

TABLE 1
Effect of Lipid-Lowering Drugs on Lipid Profile

	HDL	LDL	TG
Nicotinic acid	+15 to +35%	-5 to -25%	-20 to -50%
Fibric-acid derivatives	+10 to +35%	-5 to -20%	-20 to -50%
Statins	+5 to +15%	-18 to -55%	-7 to -30%
Thiazolidinediones	+5 to +13%	-4 to +16%	-26 to +2%
Bile acid sequestrants	+3 to +5%	-15 to -30%	-1 to +1%
Ezetimibe	+1 to +5%	-18 to -20%	-5 to -11%

The effects of currently available pharmacologic agents upon the lipid profile (8–10). Drugs that raise HDL affect other lipid parameters, increasing the difficulty of determining the effect on CHD attributable to HDL elevation alone.

HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides.

helps to make triglycerides destined for very-low-density lipoprotein (VLDL) (46). These effects of niacin cause an increase in HDL and decrease in LDL and TG, changes which have been demonstrated to reduce the complications of atherosclerotic disease.

In the Coronary Drug Project (CDP), a randomized, double-blind, placebo-controlled trial involving 8,341 men with prior myocardial infarction, which was started in 1966 (47), patients taking niacin had significantly fewer cardiovascular events and lived longer than those who received placebo (48). Niacin therapy, however, may be difficult for patients to tolerate, since it can cause flushing of the skin. Some 85% of patients taking immediate-release niacin experience flushing (49); in fact, 75% of patients in the niacin arm of the CDP dropped out of the study, mostly because of flushing (50). Slow-release niacins have reduced this side effect and have made this class of drugs more tolerable—only a quarter of patients taking the slower-release niacins experience flushing (49). Still, for those patients experiencing the problem, adhering to this regimen can be difficult. Niacin has also been criticized for making control of glucose more difficult (51); however, the CDP data suggest that this effect upon control of blood sugar does not significantly impact upon patients (48).

Fibric Acid Derivatives

Fibrate binding to peroxisome proliferator-activated receptor- α (PPAR- α) receptors causes an upregulation of a cascade of genes involved in endothelial function and RCT (29). The only fibrates currently approved for use in the U.S. are fenofibrate and gemfibrozil, but other fibrates used in

other countries include bezafibrate, ciprofibrate and clofibrate. Fenofibrate also prolongs the life-span of apoA-I, and it promotes the breakdown of VLDL, intermediate-density lipoprotein (IDL), and LDL (52). Ciprofibrate stimulates the arterial wall to give up its lipid content to HDL (53). Similar to niacin, gemfibrozil has also been shown to decrease synthesis of triglycerides and decrease apoB secretion (54). The net effect upon the lipid profile is similar to that found with niacin—decreased TG and LDL, increased HDL.

The largest trials of fibric acid derivatives in CHD patients are the CDP, which had 2,248 men with CHD on clofibrate (50); the Bezafibrate Infarction Prevention trial (BIP) with 3,090 adults with CHD on bezafibrate (55); the Helsinki Heart Study (HHS) with 4,081 hypercholesterolemic men on gemfibrozil (56); and the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) with 2,531 men with low HDL and CHD on gemfibrozil (57). While the CDP and BIP trials showed no benefit with fibrate (50, 55), the other trials did. HHS showed a one-third decrease in the incidence of CHD (56), and the VA-HIT demonstrated a 22% reduction in non-fatal myocardial infarction or death from coronary causes (57). Attributing the benefit exclusively or primarily to HDL elevation remains difficult; in the VA-HIT, for example, HDL increased by only 6%, but TG decreased by 31%. Therefore, these trials need to be carefully interpreted before one can reach a firm conclusion about the relationship between HDL and cardiovascular risk reduction.

Statins

The benefit attributable to HDL elevation is even more difficult to determine in statin trials. Statins have great ability to reduce LDL, but only limited ability to raise HDL. Furthermore, the effect on HDL differs depending on the statin, and higher doses do not necessarily translate into higher HDL. For example, in the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial, the percent increase in HDL decreased as the dose of atorvastatin (the most commonly prescribed statin in the United States) doubled (Table 2; 58). In an analysis that pooled data from 19 statin trials to examine the link between HDL and CHD, an effect of HDL on morbidity and mortality could not be determined, as the HDL effects in many of these trials were minimal (59). Nevertheless, because of their potent LDL-lowering effect, statins are the first-line treatment for dyslipidemia and for primary and secondary prevention of CHD.

TABLE 2
Change in HDL by Atorvastatin Dose

Atorvastatin Dose	HDL Increase (mg/dL ± SEM)
10 mg	2.9 ± 0.05
20 mg	2.4 ± 0.05
40 mg	2.2 ± 0.04
80 mg	1.1 ± 0.02

HDL level by atorvastatin dose in the STELLAR trial (error bars represent standard error) (58). As the dose of atorvastatin doubles, the effect upon HDL elevation declines, and the change across all doses is modest. Statins exert their effect primarily upon LDL and are not good monotherapy choices for HDL elevation alone.

SEM: standard error of the mean.

Thiazolidinediones

Thiazolidinediones (TZDs) are PPAR- γ agonists (29). TZDs make the body more sensitive to insulin, so they are primarily used to control blood sugar in Type II diabetes mellitus (DM), which makes their use particularly beneficial in addition to statin therapy for lipid management of the diabetic patient. The two TZDs approved for use in the United States—pioglitazone and rosiglitazone—affect lipids differently. While both raise HDL, pioglitazone lowers TG and has little or no effect upon LDL, whereas rosiglitazone raises LDL and has minimal effect upon TG (Fig. 6; 60). However, despite raising LDL, rosiglitazone decreased in-stent restenosis by 74% in a study of diabetic patients undergoing coronary intervention (61). Also, pioglitazone in a diabetic population and rosiglitazone in a non-diabetic CHD group were associated with decreased progression of carotid intima-media thickness (CIMT), which is correlated with decreased CHD (62, 63). However, no trial to date has demonstrated an impact of TZDs on hard endpoints such as mortality, and as with niacin and the fibrates, the TZDs' multiple other effects on hyperglycemia and LDL make it difficult to separate out their specific effect upon HDL elevation.

Bile Acid Sequestrants

Cholestyramine, colesvelam, and colestipol are bile acid sequestrants which block the absorption of bile from the gut to prevent this substrate of hepatic production of cholesterol from reaching the liver, so intestinal production of apoA-I is increased (64). In the Lipid Research Clinics Coronary Primary Prevention Trial, a study of 3,806 hypercholesterolemic men without CHD had a 19%

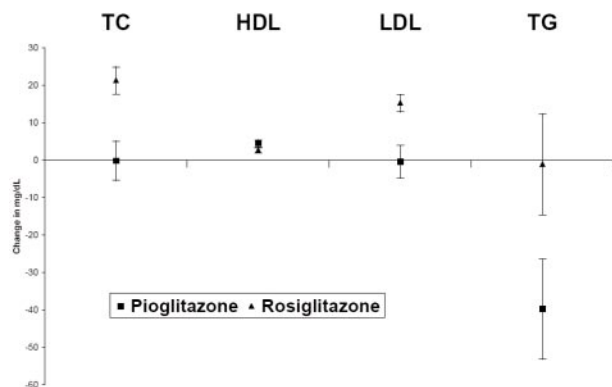


Fig. 6. Comparative effects of pioglitazone and rosiglitazone upon lipid parameters (error bars represent 95% confidence intervals) (60). Although both TZDs raise HDL and both have shown positive effects upon secondary endpoints of atherosclerotic disease, they have significantly different impacts upon LDL and TG. The clinical consequences of these differences have yet to be definitively determined by morbidity or mortality data from randomized controlled clinical trials.

TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides.

reduction in the incidence of CHD with cholestyramine (65). But these drugs can be difficult to tolerate, as gastrointestinal side effects, especially constipation, are common. Their effect upon HDL elevation, though, is negligible compared to their effect upon LDL (Table 1), so the benefits seen with these drugs are more likely due to their effect upon LDL.

Ezetimibe

Similar to the bile acid sequestrants, ezetimibe prevents intestinal cholesterol absorption, but by a different mechanism. Ezetimibe promotes efflux of dietary cholesterol and plant sterols from the intestinal wall back into the lumen, thereby decreasing cholesterol absorption (66). The effects upon HDL are modest and probably outweighed by the effect upon LDL, but it is interesting that ezetimibe also reduces atherosclerosis in animal models (67). Benefit in humans has not been conclusively demonstrated by reduction in morbidity or mortality, but for patients with difficulty controlling cholesterol with statins alone, this drug is a welcome addition.

Combination Therapy

By combining the above drugs, an additive effect upon HDL elevation has been achieved, with possible benefit. The Armed Forces Regression Study (AFREGS) examined 143 military retirees

with low HDL and CHD and found that the combination of gemfibrozil, niacin and cholestyramine increased HDL by 36%, decreased angiographic stenosis of the coronary arteries by 0.8%, and decreased cardiovascular events (death, hospitalization, cerebrovascular event or transient ischemic attack [TIA], revascularization) (68). The regression seen in coronary blockages is suggestive of RCT. The HDL-Atherosclerosis Treatment Study (HATS), another trial of patients with low HDL and CHD, found that for patients on statin-niacin combination therapy, HDL increased 26% and LDL decreased 42%, with a significant 0.4% regression of angiographic coronary stenosis and 60% reduction in major adverse cardiovascular events (69). Unfortunately this study did not compare statin-niacin to niacin or statin monotherapy, which confounds the ability to isolate the incremental benefit of niacin. However, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER)-2 study evaluated the impact of providing niacin to statin-treated patients with known CHD and moderately low levels of HDL on carotid atherosclerosis progression. The study found that the addition of niacin to statins limited atherosclerotic progression, but those on statin monotherapy increased their carotid atherosclerosis by a significant 5% (70). AFREGS, ARBITER-2 and HATS collectively suggest that HDL elevation may either stem progression or even induce regression of atherosclerotic burden.

Currently Available Alternative Treatment Options for HDL Elevation

Table 3 (71–76) lists treatments that raise HDL, but have unknown or mixed clinical benefit. Phenytoin, an antiseizure drug, raises HDL by an unknown mechanism. Observational studies suggest a cardiovascular benefit (79), and in a mouse model phenytoin reduced aortic atherosclerosis (80). However, conclusive randomized control trials have not been conducted, as the side effects of this medication—including psychomotor retardation, gingival hyperplasia, osteomalacia and coarse facies—and multiple drug-drug interactions limit the serious consideration of phenytoin as a lipid-modifying agent.

Some have speculated that the decrease in CHD among consumers of moderate amounts of alcohol, especially red wine, derived from alcohol's ability to raise HDL. It is true that alcohol elevates HDL by increasing the availability of apoA-I (81), and alcohol stimulates cellular cholesterol efflux, an early step of RCT (82). However, the American Heart Association does not recommend alcohol con-

TABLE 3
Alternative HDL-Elevating Drugs

	Change in HDL
SERM	−2 to +14%
HRT	+7 to +13%
Phenytoin	+10 to +13%
EtOH	+7 to +12%

Alternative interventions to raise HDL (71–76). These interventions have been demonstrated to raise HDL, but the clinical relevance is mixed. In the case of SERMs, some may provide cardiovascular benefit, but definitive randomized clinical trials are not yet completed. HRT, though previously assumed to be cardioprotective, has now fallen out of favor with the results of the Women's Health Initiative (WHI) study (77, 78). Phenytoin and alcohol consumption are of possible benefit but come with multiple adverse effects that limit their clinical potential in this regard.

SERM: selective estrogen receptor modulator; HRT: hormone replacement therapy; EtOH: ethanol.

sumption for cardiovascular reasons, counseling that “alcohol use should be an item of discussion between physician and patient (83).” Alcohol can also cause a host of other medical and psychological problems, so any gain for the heart has to be weighed against many other potential complications.

While National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP II) advised that hormone replacement therapy (HRT) should be considered as a treatment option for the prevention of cardiovascular disease in postmenopausal women (84), this theory has since been soundly disproven. It had been speculated that since HRT raises HDL and decreases LDL, it might be cardioprotective. However, multiple clinical trials have demonstrated that HRT actually increases cardiovascular complications (85, 86), and now HRT is no longer recommended for cardiovascular risk reduction (8).

Selective estrogen receptor modulators (SERM) also raise HDL (Table 3), and animal studies, clinical trial data, and population-based studies suggest a possible benefit (86–88). However, the effects of different SERMs vary—tamoxifen and raloxifene minimally change total HDL and increase certain HDL subfractions whereas toremifene increases total HDL (71, 89). SERMs seem to inhibit cholesterol synthesis (90). While SERMs are not currently used for the treatment of cardiovascular disease, since no trial was conducted specifically for that purpose, the Raloxifene Use for the Heart (RUTH) trial is currently underway. RUTH has enrolled 10,101 postmenopausal women with heart disease or at high risk for CHD to see if raloxifene reduces these women's CHD risk (91).

Emerging Approaches for HDL Elevation

The promise of HDL elevation as a means to further reduce the risk of CHD has attracted considerable interest, and investigations with this aim are currently underway. The drugs in most advanced development are the CETP inhibitors and apoA-I Milano.

Cholesterol Ester Transfer Protein (CETP) Inhibition

Patients with inherited CETP deficiency have elevated HDL. Homozygotes for CETP deficiency have six times the incidence of elevated HDL, and heterozygotes have twice the HDL levels of non-mutants (92). While this mutation is particularly prevalent in the Japanese population (93), and the native Japanese have the longest lifespan as a population in the world, CETP deficiency may not necessarily result in reduced CHD. In a population study of Omagiri City, Akita Prefecture in Japan, where CETP deficiency occurs 20 times more frequently than in the general population, HDL above 70 mg/dL was associated with increased CHD (94). This study also found that those over 80 years of age were less likely to have the CETP mutation, and CETP deficiency was associated with increased CHD (94). Elevated HDL secondary to CETP deficiency, therefore, may not be entirely atheroprotective. If CETP inhibition results in accumulation of lipid-laden HDL but not lipid-deficient HDL, there would be less lipid-deficient HDL to participate in RCT. On the other hand, animal models suggest that partial inhibition of CETP reduces atherosclerosis. Whether by oral small molecule (95), via vaccine-induced antibodies to CETP (96), or via anti-sense nucleotides against CETP (97), CETP inhibition resulted in reduction of atherosclerosis in rabbit models. Impressive increases in HDL have been seen in human studies of CETP inhibitors. Torcetrapib, a small molecule inhibitor of CETP, increased HDL by 46–106% (98), and JTT-705, another small molecule CETP inhibitor currently in development, increased HDL by 34% and modestly reduced LDL by 7% (99). Definitive clinical trials are underway.

apoA-I Milano

Another genetic mutation led to the development of another drug known as apoA-I Milano or ETC-216. In the village of Limone sul Garda in Italy, there are approximately 40 persons who have very low HDL (10–30 mg/dL) but nevertheless have longer

life spans than normal (100, 101). They have a mutant type of apoA-I which is now known as apoA-I Milano. Infusions of ETC-216 reduced in-stent restenosis in a pig model (44), reduced lipid content of atheromatous plaques and macrophages in a mouse model (102), and protected the *in vivo* rabbit heart from regional ischemia-reperfusion injury (103), suggesting that apoA-I Milano, as a lipid-deficient apolipoprotein, may reduce atherosclerosis by scavenging lipid from the arterial wall in RCT and by other beneficial non-RCT related effects. Weekly ETC-216 infusion in patients with acute coronary syndrome resulted in a 1.1% regression of atherosclerotic lesions after only 5 treatments, suggesting rapid RCT (104). Whether this regression will translate into reduced cardiovascular events or paradoxically increase events through plaque destabilization remains to be discovered through additional clinical trials. A limitation of apoA-I mimetics, though, is that they must be administered parenterally because gastrointestinal proteases prevent effective oral use. IV administration would limit the potential settings in which these drugs may be used, but inpatient use or administration based upon a “chemotherapy”-type outpatient model may be successful in patients with severe atherosclerotic burden.

Conclusion

The rationale for HDL elevation as a therapy for CHD appears scientifically sound and the therapy may provide a much-needed addition to the pharmacologic armamentarium. HDL plays a central role in RCT and also has antioxidant, anti-inflammatory, anti-thrombotic and endothelial-function-promoting characteristics. Via its RCT mechanism, HDL holds the promise of not only halting progression of atherosclerosis but also inducing a true regression of lesions. A number of HDL-elevating therapies are available—nicotinic acid, fibric acid derivatives, statins, TZDs, bile acid sequestrants, ezetimibe—but these drugs alter other components of the lipid profile, making clinical trial interpretation difficult in assessing the effect of HDL elevation alone. Still other available drugs raise HDL but are of dubious or uncertain clinical effect upon cardiovascular outcomes. Interventions currently in development are more specific HDL elevators, but future therapies await validation in clinical trials.

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