



ELSEVIER

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

6

Should low high-density lipoprotein cholesterol (HDL-C) be treated?



Peter P. Toth, M.D., Ph.D., Professor of Clinical Family and Community Medicine ^{a,b,*}, Marcin Barylski, M.D., Ph.D., Assistant Professor of Medicine ^c, Dragana Nikolic, MD, Doctoral Candidate ^d, Manfredi Rizzo, MD, PhD, Professor of Medicine ^{d,e}, Giuseppe Montalto, MD, Professor of Medicine ^d, Maciej Banach, MD, Professor of Medicine ^f

^aCGH Medical Center, Sterling, IL 61081, USA

^bUniversity of Illinois School of Medicine, Peoria, IL, USA

^cDepartment of Internal Medicine and Cardiological Rehabilitation, Medical University of Lodz, Lodz, Poland

^dBiomedical Department of Internal Medicine and Medical Specialties University of Palermo, Palermo, Italy

^eEuro-Mediterranean Institute of Science and Technology, Palermo, Italy

^fNephrology and Hypertension, Medical University of Lodz, Zeromskiego 113, 90-549 Lodz, Poland

Keywords:

coronary artery disease
fibrate
high-density lipoproteins
low-density lipoproteins
niacin
reverse cholesterol transport
statin
thiazolidinedione

The first observations linking a low serum level of HDL-C to increased risk for cardiovascular disease were made over 50 years ago. High serum levels of HDL-C appear to protect against the development of atherosclerotic disease, while low serum levels of this lipoprotein are among the most important predictors of atherosclerotic disease in both men and women and people of all racial and ethnic groups throughout the world. It has long been assumed that therapeutic interventions targeted at raising HDL-C levels would lower risk for such cardiovascular events as myocardial infarction, ischemic stroke, and death. Even after five decades of intensive investigation, evidence to support this assumption has been fleeting. A number of *post hoc* analyses of randomized controlled trials and meta-analyses suggest that HDL-C raising, particularly when coupled with aggressive LDL-C reduction, impacts risk for cardiovascular events and rates of progression of atherosclerotic disease. Unfortunately, four recent prospective trials

* Corresponding author. University of Illinois School of Medicine, Peoria, IL, USA. Tel.: +1 (815) 632 5093; Fax: +1 (815) 626 5947.

E-mail addresses: peter.toth@cghmc.com (P.P. Toth), mbarylski3@wp.pl (M. Barylski), draggana.nikolic@gmail.com (D. Nikolic), manfredi.rizzo@unipa.it (M. Rizzo), giuseppe.montalto@unipa.it (G. Montalto), maciejbanach@aol.co.uk (M. Banach).

performed with the intent of testing the “HDL hypothesis” (ILLUMINATE, dal-OUTCOMES, AIM-HIGH, and HPS2-THRIVE) failed to meet their primary composite endpoints. These results have led many clinicians and investigators to question the validity of the assumption that HDL-C raising reduces risk for cardiovascular events. Additional trials with other drugs are underway. In the meantime, HDL-C cannot be considered a target of therapy. Given the complexity of the HDL proteome and lipidome, there is biological plausibility for how HDL particles might exert atheroprotection. We explore the evidence supporting the inverse relationship between HDL-C and cardiovascular disease risk, documented mechanisms by which HDL particles may exert atheroprotection, and the findings either supporting or negating specific therapeutic interventions in patients afflicted with low HDL-C.

© 2013 Elsevier Ltd. All rights reserved.

Introduction

The etiologic role of low-density lipoprotein cholesterol (LDL-C) in atherosclerotic disease and the reduction in risk for cardiovascular (CV) events associated with lipid-modifying therapies that lower LDL-C are highly established. It is also recognized that low serum levels of high-density lipoprotein cholesterol (HDL-C) are among the most important predictors of risk for developing coronary artery disease (CAD) and its sequelae, such as myocardial infarction (MI), stroke, and death [1]. In contrast, high serum levels of HDL-C appear to be atheroprotective and correlate with reduced risk for CV morbidity and mortality. Considerable basic scientific research has suggested that HDL particles may possibly exert a number of antiatherogenic effects. From a clinical perspective, it would seem to be self-evident that simply raising HDL-C by pharmacologic or lifestyle means would reduce risk for developing CAD and sustaining CV events. Unlike the narrative for LDL-C, that for HDL-C has not played out quite so simply. A number of recent clinical trials that purportedly tested the “HDL hypothesis” failed to meet their primary composite endpoints. In addition, a Mendelian randomization study showed that a variety of alleles associated with serum HDL-C levels do not correlate significantly with risk for CAD [2].

Newer studies demonstrate that the roles of HDL in lipid and lipoprotein metabolism are far more complex than previously thought. Punctuating this complexity, over the last five years the literature on HDL has become populated with inconsistencies and contradictions. There is much about this lipoprotein and its range of activity that we still do not adequately understand. For years, many investigators have argued that serum levels of HDL-C should be a therapeutic target. Given the totality of evidence that has accrued over the last five decades, the primary questions explored herein are: (1) is there demonstrable clinical benefit treating patients with low serum levels of HDL-C with lipid-modifying drugs; and (2) more specifically, should drugs be used to raise low serum levels of HDL-C? These are distinct and mutually exclusive questions.

There is evidence from subgroup analyses in multiple clinical trials that treating patients with low serum levels of HDL-C with lipid modifying drugs is efficacious. Although there is suggestive evidence that raising HDL-C *per se* impacts CV risk and reduces rates of atherosclerotic disease progression in both the carotid and coronary vasculature, this is based on *post hoc* secondary analyses and a number of meta-analyses. There is no primary evidence to date from randomized controlled clinical trials that HDL-C is a target of therapy or that raising HDL-C to some threshold level either through lifestyle modification or pharmacologic intervention reduces risk for CV events. A more comprehensive evaluation of the controversies surrounding HDL-C and its role in patient management was recently published [3].

Epidemiology

Prospective cohorts evaluated around the world consistently demonstrate that there is an inverse relationship between HDL-C and risk for CV events in both men and women and people irrespective of

race or ethnicity. Different studies adopt different approaches to adjusting for established risk factor covariates, but, despite this, low HDL-C consistently emerges as an independent risk factor for CV morbidity and mortality. The Cooperative Lipoprotein Phenotyping Study included 6859 men and women from five areas of the United States (US). An inverse relationship between HDL-C levels and CHD prevalence remained significant even after adjusting for LDL-C and triglyceride levels [4]. An inverse relationship between HDL-C and CHD risk was also observed in the Tromsø Heart Study which included 6595 men 20–49 years of age [5]. A low serum HDL-C in this population was associated with a 3-fold greater risk for CAD than an elevated LDL-C. In the Münster Heart Study (PROCAM), an HDL-C concentration <35 mg/dL was associated with a 3-fold greater risk for developing CAD compared with participants whose HDL-C concentrations >35 mg/dL [6]. The association between CAD risk and HDL-C was independent of other cardiovascular disease risk factors. The SCORE dataset includes seven pooled European studies with a total of 104,961 participants. Among Europeans, elevated HDL-C correlated with reduced CV morbidity and mortality irrespective of age, gender, or level of calculated baseline risk [7]. The AMORIS study evaluated the relationship between HDL-C and CV risk in approximately 160,000 men and women [8]. A significant, independent inverse relationship was noted in both men and women. In the Copenhagen Heart Study, when comparing participants in the first to the fifth quintile of HDL-C, the hazard ratio for developing ischemic heart disease is approximately 3.0 [9]. Among Asians a large meta-analysis suggests that compared to participants with a normal lipid profile, isolated low HDL-C increases risk for CV events by 67% [10]. The Emerging Risk Factors Collaboration further demonstrated that the inverse relationship between HDL-C and CV risk remains significant even after adjusting for non-HDL-C (defined as total cholesterol minus HDL-C, a surrogate measure of total atherogenic lipoprotein burden in serum) [11]. The inverse relationship between HDL-C and CV risk is particularly striking in men with established CAD. After 10 years of follow-up in the Lipid Research Clinics study, the hazard ratio for CV mortality increased incrementally and significantly (3.3, 11.8, and 18.3 for men in HDL-C tertiles >45, 35–44, and <35 mg/dL, $p < 0.001$ for trend) [12].

The excess risk attributable to a low HDL-C, irrespective of LDL-C levels, is illustrated by the Framingham Heart Study. In any given tertile of LDL-C the relative risk of a CAD-related event increases as HDL-C levels decrease, even among participants whose baseline LDL-C <100 mg/d [13]. In contrast, a 50% reduction in CHD risk over 8 years of follow-up was observed for every 20 mg/dL increase in HDL-C [14]. A meta-analysis of 4 prospective US studies (Framingham Heart Study, Lipid Research Clinics Prevalence Mortality Follow-up Study, Coronary Primary Prevention Trial, and Multiple Risk Factor Intervention Trial), demonstrated that a 1 mg/dL increase in HDL-C is associated with a 2% decrease in CHD risk for men and a 3% decrease for women [15]. Among Japanese men living in Osaka, a 1 mg/dL increase in HDL-C correlates with a 6.4% lower risk of myocardial infarction (MI) and a 5.7% lower risk of CHD [16]. The relative risk for MI or CAD was 3.39 and 4.17, respectively, when comparing men in the lowest and highest quartiles of HDL-C.

In general, a low HDL-C is an adverse prognostic indicator even among individuals with very low LDL-C. In the Physicians' Health Study, the lowest risk for MI was observed in men with the highest HDL-C and lowest total cholesterol levels [17]. On a background of statin treatment in the Treating to New Targets (TNT) study, HDL-C was still predictive of major cardiovascular events in patients with LDL-C <70 mg/dL [18]. In a retrospective analysis of a group of Veterans Administration patients with LDL-C values <60 mg/dL at baseline, a 10% increase in MI or hospitalization for ischemic heart disease was observed for every 10 mg/dL decrease in HDL-C [19]. In an important meta-analysis, it was shown that, although statin therapy reduces risk for CV events at all baseline levels of HDL-C, it does not alter the inverse relationship between HDL-C and CV risk [20]. One exception to these findings comes from the JUPITER trial. Ridker and coworkers found that among patients treated with rosuvastatin 20 mg/day (with a mean attained LDL-C of approximately 60 mg/dL), in a multivariate analysis on-treatment HDL-C was no longer predictive of CV events [21].

The relationship between low HDL-C and CV risk is also discernible in older patients. The Cardiovascular Health Study was a cohort of elderly persons in the US (1954 men and 2931 women aged 65 and older who were at risk for MI or stroke) and evaluated the relationships between lipid parameters and risk for MI, ischemic stroke, and mortality over 7.5 years of follow-up [22]. The associations between total cholesterol/LDL-C and MI or ischemic stroke were only marginally significant. HDL-C, however, was inversely associated with MI risk (hazard ratio = 0.85 per 15.7 mg/dL). High serum levels of HDL-C were

also associated with a decreased risk for ischemic stroke in men, but not women. In the Northern Manhattan Stroke Study, elevated HDL-C reduced risk of stroke in participants older than 75 years irrespective of race or ethnicity according to a dose–response relationship [23]. Among Dutch patients ≥ 85 years of age, risk for CV mortality or stroke was independent of serum LDL-C but highly associated with low HDL-C [24]. In a study evaluating 3904 men and women older than 71 years, low HDL-C levels were a better predictor of CV morbidity and mortality than total cholesterol [25]. When comparing participants with an HDL-C of < 35 mg/dL to those with an HDL-C > 60 mg/dL, the relative risk for CHD mortality was 4.1.

Serum concentrations of HDL-C correlate with atherosclerotic disease progression and CV events in patients who undergo percutaneous transluminal coronary artery stenting. In a coronary imaging study which included 1952 men and women aged 25–82 years who had at least 1 plaque present in the right carotid artery at baseline plaque progression was quantified over 7 years of follow-up [26]. In a multi-variable adjusted model, HDL-C, systolic blood pressure, age, and smoking status were independent predictors of atheromatous plaque progression. For every 15.6 mg/dL reduction in HDL-C, the mean plaque area of target lesions increased significantly by 0.93 mm². In a study of Japanese patients with CAD treated with pravastatin, increases in on therapy serum HDL-C levels were associated with reductions in atheromatous plaque volume; however, reductions in serum LDL-C and TC did not impact rates of plaque progression [27]. Among patients who have undergone drug-eluting stent implantation, low serum HDL-C was highly predictive of a three-fold increased risk of mortality at both 1 month and between 1 and 12 months of follow-up. These investigators showed that for every 1 mg/dL elevation in HDL-C, risk of mortality decreased by 4% [28]. Among patients who have undergone coronary artery bypass grafting, low serum HDL-C portends significantly reduced survival after 10 and 15 years of follow-up [29]. An exception to these findings is a *post hoc* analysis of patients from the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study which found that higher HDL-C levels were associated with progressively higher levels of risk for major coronary events in patients with established CAD [30]. A more recent analysis of the Framingham Offspring cohort suggests that low HDL-C levels only increase risk in patients with concomitant insulin resistance [31]. Participants with low HDL-C (mean 42 mg/dL) but no evidence for insulin resistance have a level of risk for CAD events similar to those with high HDL-C (mean 62 mg/dL) and no insulin resistance. These findings await confirmation or negation from other cohorts.

Prevalence of low HDL-C

Low serum levels of HDL-C are defined as < 40 mg/dL in men and < 50 mg/dL in women. The difference arises from the well-known observation that women have on average a 10 mg/dL higher serum HDL-C compared to age-matched men. According to analysis of NHANES data for the period 2003–2006, 23% (46.4M) of US adults have low HDL-C, 6% (11.6M) of US adults have low HDL-C coupled with both high LDL-C and triglycerides, 29% have hypertriglyceridemia (58.9 million), and approximately 6.6% (13.1 million) adults have both low HDL-C and hypertriglyceridemia [32]. Low HDL-C prevalence increases with body mass index (BMI), reduced physical activity, cigarette smoking, and insulin resistance. In the US low HDL-C is most prevalent among Mexican American men and women compared to non-Hispanic black or white persons [33]. The presence of cardiovascular disease or cardiovascular risk factors increases the likelihood for diagnosing low HDL-C, especially in patients with diabetes mellitus or metabolic syndrome [34]. These two populations are prone to development of “atherogenic dyslipidemia” characterized by elevations in triglycerides and decreases in HDL-C that may be accompanied by increased levels of apolipoprotein B (apoB) and non-HDL-C. Poor glycemic control has been linked to low HDL-C in patients with type 2 diabetes, with a 1% increase in glycosylated hemoglobin (HbA_{1c}) conferring a 17% increased risk of low HDL-C, independent of other risk factors [35]. Diabetic retinopathy also has an independent association with low HDL-C [36]. Patients with CAD have a high prevalence of low HDL-C, and among those with LDL-C levels of 70–100 mg/dL or < 70 mg/dL the prevalence is 66% and 79%, respectively [37]. Currently, 13% of US adults have diabetes mellitus and 34% meet the Third National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) criteria for metabolic syndrome [38,39]. As the obesity epidemic continues to plague the US and other regions throughout the world, the prevalence of type 2 diabetes, metabolic syndrome, and low HDL-C will also rise. In Europe the prevalence of low HDL-C is also quite substantial, ranging from 30% (France) to 49% (The Netherlands) [40]. The incidence of low HDL-C among Turkish people is among the highest in the world [41].

Biological functions of HDL

Is the inverse association between HDL-C and risk for CAD biologically plausible? Yes. The HDLs are capable of mediating a number of antiatherogenic functions due to the complex constitution of their proteome and lipidome. The HDLs carry a large variety of enzymes, apoproteins, globulins, microRNAs, bioactive lipids, acute phase reactants, and complement components, among other molecules [3,42]. Many of these molecular species confer different types of functionality to HDL particles. The molecular cargo of HDL particles confers extraordinary complexity to this lipoprotein class and makes their comprehensive characterization scientifically quite challenging. The molecular cargo of HDL particles can change in response to alterations in the metabolic milieu (sepsis, chronic inflammation, infection, etc). The apoB-containing lipoproteins (eg, LDL, very low-density lipoprotein, and intermediate-density lipoprotein) promote atherosclerosis by delivering cholesterol and phospholipids into the subendothelial space. In contrast, HDL particles promote the clearance of lipids from the subendothelial space and intima through a series of reactions defined as reverse cholesterol transport (RCT) [43]. During RCT, HDL promotes the mobilization of cholesterol from the periphery and facilitates its translocation to the liver for elimination or to steroidogenic organs for hormone biosynthesis (Fig. 1). According to the RCT hypothesis, if HDL is not present in sufficient concentrations or does not interact properly with macrophage-derived foam cells and hepatocytes, intravascular cholesterol accumulates and fosters the development of atherosclerosis. The capacity of HDL to promote macrophage cholesterol externalization was recently shown to impact risk for CAD.

In addition to its key role in cholesterol homeostasis, the HDLs have been shown to impact multiple pathways in *in vitro* settings that are potentially atherogenic (Fig. 2). The HDLs activate a variety of intracellular signaling systems within endothelial cells, macrophages, and platelets [44]. The biological relevance of some of these activities are intriguing but not yet established *in vivo*. HDL positively impacts endothelial function and has antithrombotic, anti-inflammatory, and antioxidant activities [45]. HDL has been shown to oppose some of the abnormalities associated with endothelial dysfunction, such as reduced nitric oxide production and upregulation of adhesion molecule (e.g., vascular cell adhesion molecule-1, intercellular adhesion molecule-1) expression. HDL stimulates endothelial cell proliferation and migration and inhibits the apoptosis of these cells, helping to maintain vascular wall structure and function. Through a variety of signaling mechanisms, HDL reduces platelet reactivity and aggregability, possibly reducing the risk for thrombus formation [46]. Due to the activities of HDL-associated enzymes (paraoxonase, glutathione peroxidase, and platelet-activating factor-acetylhydrolase) and apoprotein constituents (apoprotein A-I and A-II which possess redox active methionine residues), HDL mediates antioxidant activities, including inhibition of fatty acid and phospholipid oxidation in LDL particles [47]. Oxidized LDL is proatherogenic: it activates macrophage lipid scavenging, induces endothelial dysfunction, and promotes inflammation in the subendothelial space. HDLs have also been shown to stimulate islet cell insulin secretion, participate in immunity, and sequester endotoxin, among other functions [48].

The HDLs are highly heterogeneous and evidence is mounting that different HDL species have varying proteomes and functional profiles. It must be emphasized that, in contrast to epidemiologic studies, it is not the cholesterol in the HDL fraction that is atheroprotective; rather, it is the number of functional particles capable of driving RCT and rendering beneficial effects along arterial walls that likely determine the magnitude of protection from atherogenesis. The capacity of HDL to promote macrophage lipid mobilization and externalization is an independent risk factor for CAD [49]. The functionality of HDL particles is a matter of growing investigation. A variety of functionality assays are in development and await validation [3]. In patients with systemic infections, chronic inflammatory states, CHD, recent acute coronary syndromes, diabetes mellitus, and chronic kidney disease, the molecular cargo of HDL can be converted from an atheroprotective to a pro-oxidative and pro-inflammatory state [50,51]. Under these circumstances, the apoprotein and enzyme constituents of HDL can be replaced by acute phase reactants (serum amyloid A, fibrinogen), which attenuates the capacity of HDL to participate in RCT or mediate other antiatherogenic functions. Such observations highlight the need to therapeutically target HDL function rather than simply try to bolster serum levels of HDL-C.

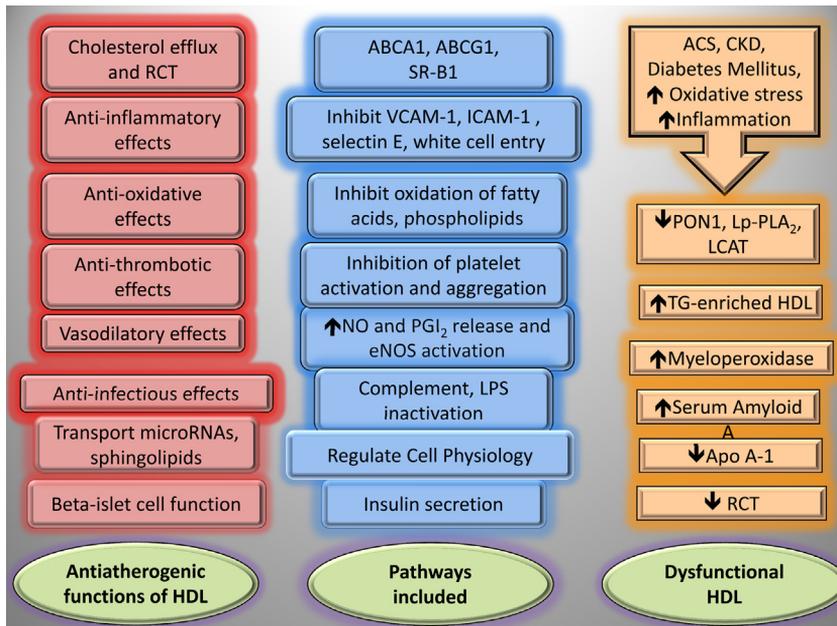


Fig. 2. Summary of antiatherogenic effects of HDL with pro-atherogenic properties of dysfunctional HDL. (Abbreviations: ABCA1, adenosine triphosphate binding cassette transporter 1; ACS, acute coronary syndrome; Apo A-1, apoprotein A1; CKD, chronic kidney disease; eNOS, endothelial nitric oxide synthase; HDL, high-density lipoprotein; ICAM-1, intercellular adhesion molecule 1; LCAT, lecithin: cholesterol acyltransferase; MPO, myeloperoxidase; Lp-PLA₂, lipoprotein-associated phospholipase A₂; LPS, bacterial lipopolysaccharide; NO, nitric oxide; PGI₂, prostacyclin; PON1, paraoxonase 1; RCT, reverse cholesterol transport; SR-BI, scavenger receptor BI; SAA, serum amyloid A; VCAM-1, vascular cell adhesion molecule 1.

reduced risk for CV event. In patients on usual dose lipid-lowering medication ($N = 1910$), every 3.8 mg/dL increase in HDL-C was associated with a 6% reduction in CV events. However, consistent with the JUPITER trial, in patients treated with intensive lipid-lowering treatment ($N = 2046$), HDL-C levels did not correlate with risk of CV events at any level of attained LDL-C. This is in sharp contrast to a *post hoc* analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, which evaluated the impact of optimal medical therapy on CV outcomes in patients with stable ischemic heart disease [53]. For the entire cohort the rate of nonfatal MI and death was 33% lower in the highest HDL-C quartile compared to the lowest quartile. HDL-C levels were predictive of CV events at any level of LDL-C. Among patients who achieved LDL-C < 70 mg/dL, those in the highest quintile of HDL-C had a significant 65% relative risk reduction in MI and mortality compared to the lowest quintile.

Meta-analyses

The clinical impact of therapeutically raising HDL-C on cardiovascular morbidity and mortality is a subject of robust debate. Lipid modifying therapies impact multiple lipoprotein fractions. The precise impact of small elevations in HDL-C on CVD risk can be difficult to quantify. Meta-analyses designed to ascertain the impact of HDL-C raising on hard CV endpoints are decidedly mixed. One meta-analysis conducted by Briel and colleagues included 108 randomized clinical trials (including statins, fibrates, niacin, and combinations of lipid modifying drugs) that enrolled nearly 300,000 men and women [54]. After adjustment for changes in LDL-C, no association was found between HDL-C elevation and risk of nonfatal MI, CHD mortality, or all-cause mortality. One limitation is that the mean increase in HDL-C was only 1.7 mg/dL, a change that may be too small to yield significant reductions in CV event rates. Another meta-analysis that included only randomized controlled trials of fibrates ($n = 53$) or niacin

($n = 30$) with HDL-C elevations of 4.1 mg/dL (10%) and 6.7 mg/dL (16%), respectively [55]. These changes were associated with reductions in risk of major coronary events by 25% and 20%, respectively, with fibrates and niacin. A more recent meta-analysis of the niacin trials suggested overall benefit from the drug, but the benefit did not correlate with magnitude of change in HDL-C [56].

A meta-analysis of 4 prospective randomized statin IVUS trials revealed that increases in HDL-C independently predicted atheroma regression [57]. The greatest benefit was observed among patients who achieved an LDL-C < 87.5 mg/dL and an increase in HDL-C of at least 7.5%. The individual trials included in this meta-analysis were not powered to evaluate the effect of treatment on cardiovascular event rates. Another analysis of 7 large statin trials that evaluated coronary atherosclerotic disease by quantitative coronary angiography found a significant relationship between atherosclerotic plaque regression and on-treatment elevations in HDL-C [58]. It is unknown if regression of atherosclerotic disease correlates with reductions in cardiovascular morbidity and mortality. An analysis of 23 randomized controlled trials substantiates the importance of simultaneously raising HDL-C and reducing LDL-C [59]. The relationship between the sum of the percent HDL-C increase and percent LDL-C decrease and (1) reductions in cardiovascular morbidity and mortality and (2) change from baseline in mean proximal percent stenosis on quantitative coronary angiography is linear. These meta-analyses do not prove that raising HDL-C is beneficial, as they must be considered hypothesis generating only. Definitive proof must come from randomized controlled trials of lipid-modifying therapy.

Statins

The statins induce elevations in HDL-C by two principal mechanisms. First, the statins inhibit factor Rho, which leads to activation of peroxisome proliferator-activated receptor- α (PPAR- α) and increased hepatic expression of apo A-I and apo A-II, resulting in increased HDL biogenesis [60]. Second, by decreasing serum VLDL and triglyceride levels, the statins reduce the amount of triglycerides transferred into HDL particles by CETP, thereby reducing HDL catabolism by hepatic lipase [61]. In efficacy studies, the statins raise HDL-C by approximately 5–13%.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) enrolled 6605 healthy men and women with average LDL-C and below average HDL-C [62]. Participants with baseline HDL-C < 45 mg/dL experienced a 45% relative risk reduction for CV events, while the risk reduction for those with baseline HDL-C > 45 mg/dL was 15%. In this trial risk reduction was maximized when patients experienced HDL-C increases of >7.5% coupled with reductions in LDL-C [63]. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial enrolled 5804 patients age 70–82 years of age [64]. Significant reductions in the primary composite endpoint (coronary death, nonfatal MI, or stroke) were only observed in the group with baseline HDL-C concentrations <43 mg/dL. Regression of atheromatous plaque as measured by quantitative coronary angiography in the Lipoprotein and Coronary Atherosclerosis Study (LCAS) was only significant for patients with baseline HDL-C less than 35 mg/dL [65]. Although none of these studies were specifically designed to evaluate the impact of statin therapy with low baseline HDL-C, they do suggest that statin therapy is beneficial in this subgroup.

Clinical Recommendation: In patients with isolated low HDL-C or low HDL-C coupled with elevated LDL-C, statin therapy can be considered based on subgroup analyses of AFCAPS/TexCAPS, PROSPER, and LCAS.

Fibrates

Fibric acid derivatives (fibrates) are synthetic PPAR- α agonists that influence HDL metabolism. Fibrates, on average, raise serum HDL-C approximately 10% [66]. The fibrates stimulate hepatic HDL production and lipidation by upregulating the expression of hepatic apo A-I and A-II. The fibrates stimulate RCT by increasing macrophage expression of ABCA1 and hepatocyte SR-BI [67]. The fibrates stimulate triglyceride catabolism by increasing the activity of lipoprotein lipase (LPL) in serum. As the triglycerides in VLDL particles and chylomicrons undergo catabolism, surface coat mass (phospholipids and apoproteins) is released and is used to assimilate HDL in serum. Low LPL activity is associated with

hypertriglyceridemia and hypoalphalipoproteinemia. By reducing serum levels of triglycerides, the fibrates decrease HL dependent catabolism of HDL particles.

The results of clinical trials with fibrates have been mixed, but fibrates (particularly gemfibrozil) have been shown to reduce the rate of atheromatous plaque progression as well as the risk for CHD-related events [68,69]. A meta-analysis of 18 placebo-controlled fibrate trials found that fibrate therapy reduces the relative risk of major cardiovascular events by 10% and relative risk of coronary events by 13%, but does not reduce the risk of ischemic stroke or mortality [70]. In the Helsinki Heart Study, treatment with gemfibrozil 1200 mg/day reduced cardiovascular event rates by 34% in asymptomatic middle-aged men with dyslipidemia compared with placebo [71]. It was estimated that every 1% increment in on-treatment HDL-C yielded a 3% reduction in CHD events. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) randomized a high risk patient population—2531 men with CHD, low HDL-C (≤ 40 mg/dL; mean baseline 31 mg/dL), and moderate LDL-C (≤ 140 mg/dL; mean baseline 111 mg/dL) [72]. With a median follow-up of 5.1 years, gemfibrozil (1200 mg/day) was associated with a 22% reduction in the primary composite endpoint (nonfatal MI or CV death) and a 24% reduction in the composite of CV death, nonfatal MI, and ischemic stroke. For each 5 mg/dL increment in HDL-C, it was estimated that CHD events were reduced by 11%.

The Bezafibrate Infarction Prevention (BIP) randomized 3090 patients with a history of MI or stable angina to either bezafibrate or placebo [73]. The primary composite of CV events was reduced by a nonsignificant 9%. However, among patients with metabolic syndrome (all of whom had low HDL-C), risk for any MI or fatal MI decreased by 29% and 33%, respectively [74]. After a median follow-up of 7.9 years, it was shown that each 5 mg/dL increment in HDL-C was associated with a 27% reduction in risk of nonfatal MI and CV mortality [75]. After 16-years of follow-up, a 22% reduction in mortality was observed among patients in the highest tertile of HDL-C response treated with bezafibrate. [76] *Post hoc* analyses of two negative trials (the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, suggest that among diabetic patients with high triglycerides and low HDL-C, fenofibrate therapy may reduce risk for CV events [77,78].

Clinical Recommendation: In patients with low HDL-C and hypertriglyceridemia, fibrate therapy can be considered based on subgroup analyses of the Helsinki Heart Study, BIP, FIELD, and ACCORD trials. VA-HIT shows that in patients with low HDL-C and modestly elevated LDL-C (mean 111 mg/dL), gemfibrozil therapy is efficacious as monotherapy. However, given current guideline recommendations, statin therapy is first-line therapy in these patients and gemfibrozil is generally contraindicated for use in combination with a statin.

Niacin

Niacin (nicotinic acid) binds with high affinity to a receptor on both adipocytes and macrophages. The human and murine isoforms of this receptor are referred to as HM74 and PUMA-G (protein-upregulated in macrophages by interferon- γ) [79]. The natural ligand for these receptors is not yet identified. When niacin binds to this receptor in adipose tissue, hormone-sensitive triglyceride lipase is inhibited. As adipocyte lipolysis decreases, less fatty acid is released from triglyceride stores. This decreases the amount of fatty acid delivered to the liver, which reduces hepatic VLDL secretion and serum triglyceride levels. HDL-C levels will rise because of reduced triglyceride enrichment by CETP and less catabolism of HDL particles by HL. Niacin upregulates ABCA1 expression on the surface of macrophages. This would be expected to increase rates of HDL formation as well as the rate of RCT [80]. Niacin also reduces hepatic clearance of HDL particles and promotes the formation of large cholesteryl ester-enriched HDL particles.

Niacin is the most efficacious of currently available agents for raising HDL-C levels, increasing HDL-C by as much as 25%–30% (Table 1). Both as monotherapy and in combination with a statin, niacin reduces cardiovascular events. In the Coronary Drug Project, niacin 3.0 g daily reduced risk for stroke (24%), MI (26%), and revascularization (67%) compared to placebo in men with established CHD [81]. The Familial Atherosclerosis Treatment Study (FATS) randomized men ($n = 146$) to treatment with colestipol and niacin, colestipol and lovastatin, or usual care [82]. After 2.5 years, combination treatment was associated with significant decreases in coronary stenosis and a substantial 73% relative

Table 1
Increases in HDL-C mediated by pharmacologic agents.

Intervention	Increase in HDL-C
Niacin	16%–30%
Fibrates	~10%
Statins	5%–13%
Thiazolidinediones	8%–16%

reduction in death, MI, or refractory ischemic symptoms requiring surgical or interventional treatment. The Armed Forces Regression Study (AFREGS) randomized 143 patients with CAD and HDL < 40 mg/dL (mean 34 mg/dL) to placebo or HDL-C raising treatment with gemfibrozil, niacin, and cholestyramine. [83] After thirty months, the patients treated with triple combination therapy experienced a reduction in risk for coronary stenosis ($P = 0.03$) and a 50% reduction in cardiovascular morbidity and mortality. The HDL Atherosclerosis Treatment Study (HATS) showed that the combination of simvastatin and niacin reduced the risk of the composite primary endpoint (coronary mortality, MI, stroke, and revascularization) and prevented atherosclerotic plaque progression in a population of patients with CHD and low HDL-C (mean baseline 34 mg/dL) [84].

A number of studies show niacin reduces carotid atherosclerosis in high-risk patients with low HDL-C who were on statin therapy [85,86]. The ARBITER 6–HALTS trial compared extended-release niacin and ezetimibe as add-ons to statin monotherapy in patients with CHD or CHD risk equivalents [87]. The study was terminated early based on an interim analysis suggesting superiority of niacin over ezetimibe for reduction in carotid intima-media thickness (CIMT). Changes in HDL-C levels likely influenced the disparate outcomes between the two groups. Mean HDL-C increased by 7.5 mg/dL with niacin treatment and decreased by 2.8 mg/dL with ezetimibe treatment.

AIM-HIGH randomized 3414 men and women (mean age 64 years) with CAD on background statin with or without ezetimibe to extended-release niacin versus placebo [88]. The primary endpoint was defined as time to first event for the composite of CHD death, non-fatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary or cerebral revascularization. The hypothesis of the trial was that raising HDL-C with extended-release niacin (ERN) would decrease CV events in patients with LDL-C of 40–80 mg/dL. Baseline lipids included LDL-C 71 mg/dL, non-HDL-C 106 mg/dL, apo B 80 mg/dL, and HDL-C 35 mg/dL. The trial was terminated early when the Data Safety Monitoring Board deemed it would be futile to continue due to near superimposability of the Kaplan–Meier outcome curves for the two treatment groups. The primary endpoint occurred in 282 ERN-treated subjects (16.4%) versus 274 placebo-treated patients (16.2%). In a *post hoc* analysis, it was shown that among patients with baseline triglycerides ≥ 200 mg/dL and HDL-C < 32 mg/dL, risk for the primary endpoint was reduced significantly by 37%.

The Second Heart Protection Study (HPS-2 THRIVE) comparing simvastatin/extended-release niacin/laropiprant versus simvastatin alone enrolled 25,673 high-risk patients with a history of MI or CAD, cerebrovascular atherosclerotic disease, peripheral arterial disease, or diabetes mellitus [89]. At baseline patients were being treated with either simvastatin 40 mg daily or ezetimibe/simvastatin 10/40 mg daily. The extended-release niacin used in HPS-2 THRIVE was combined with laropiprant, a prostaglandin D-2 antagonist in order to reduce the intensity of niacin-induced-flushing. The primary endpoint included non-fatal MI or coronary death, stroke (non-fatal or fatal stroke), or need for revascularization (coronary or non-coronary artery surgery, angioplasty, or including amputation). Baseline lipid profiles included LDL-C 63 mg/dL, HDL-C 44 mg/dL, and triglycerides 125 mg/dL. After 4 years of follow-up there were no significant between groups differences observed. No HDL-C or triglyceride subgroups experienced benefit.

Clinical Recommendation: Based on the results of AIM-HIGH and HPS-2 THRIVE, if a high risk patient's LDL-C and non-HDL-C are already at risk stratified targets, there is no incremental benefit when niacin is added to ongoing therapy with a statin \pm ezetimibe. However, based on AIM-HIGH, if a patient has triglycerides ≥ 200 mg/dL and HDL-C < 32 mg/dL, then there may be benefit, although no benefit was discernible in this group in HPS-2 THRIVE. In studies such as FATS and AFREGS, it is difficult to discern how much benefit is attributable to niacin given the complex pharmacologic regimens used. In

HATS, there was no statin monotherapy arm to compare statin/niacin combination therapy to. There are no data to support the administration of niacin with or without statin therapy in patients with isolated low HDL-C.

Thiazolidinediones

Thiazolidinediones (TZDs) are used to promote insulin sensitization in patients with type 2 diabetes mellitus. Insulin resistance adversely impacts lipid metabolism. These drugs are PPAR- γ agonists that impact both glucose and lipid metabolism. The effect of these agents on lipids is variable. However, by relieving insulin resistance, the TZDs can decrease serum VLDL/triglycerides, increase the buoyancy of LDL particles, and increase serum levels of HDL-C. The TZDs have also been shown to increase macrophage expression of ABCA1 and ABCG1 by agonizing LXR- α [90]. When comparing pioglitazone and rosiglitazone in 802 patients with type 2 diabetes and dyslipidemia, pioglitazone 45 mg/day increased HDL-C by 14.9%, whereas rosiglitazone 4 mg twice daily increased HDL-C by 7.8% ($p < 0.001$) [91]. These data are in agreement with an earlier meta-analysis showing significantly greater HDL-C elevation with pioglitazone compared with rosiglitazone [92].

Pioglitazone has been shown to slow the progression of atherosclerotic disease in both the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial [93] and the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial [94] and reduce the risk of adverse cardiovascular outcomes and all-cause mortality [95]. The favorable effects of pioglitazone on atherosclerotic disease progression in both the PERISCOPE and CHICAGO trials was, in part, attributed to on-therapy increases in HDL-C. The TZDs are currently not indicated for use in nondiabetic patients with insulin resistance (e.g., patients with metabolic syndrome).

Clinical Recommendation: At the present time, the TZDs do not have an indication for treating lipids or for managing low HDL-C. In patients with diabetes, the TZDs do impact HDL metabolism and this appears to contribute to reductions in risk for atherosclerosis progression. There are no data to suggest that the increase in HDL-C induced by TZDs impacts CV risk.

Cholesteryl ester transfer protein inhibitors

Torcetrapib was the first cholesteryl ester transfer protein (CETP) inhibitor to be used in a large-scale clinical trial. The ILLUMINATE trial failed to show benefit from the drug and the clinical trial was brought to a sudden and unexpected halt because of a 58% significant increased risk of death due to any cause in subjects randomized to torcetrapib despite the fact that torcetrapib increased HDL-C 72.1% and decreased LDL-C by 24.9% compared to baseline levels ($p < 0.001$) [96]. The increase in mortality among patients randomized to torcetrapib is thought to represent off-target effects (increases in blood pressure and induction of electrolyte disturbances). Patients with familial hypercholesterolemia treated with torcetrapib in the RADIANCE 1 study did not demonstrate regression in carotid intima media thickness despite a 55.5% increase in HDL-C [97]. There was also progression of disease in the common carotid segment, raising the concern of a directly toxic effect of torcetrapib on the endothelium. In the RADIANCE 2 trial, patients with mixed dyslipidemia also had a similar increase in HDL-C, without an effect on carotid intima media thickness [98]. Consistent with findings in the ILLUMINATE trial, torcetrapib was associated with elevations in blood pressure.

A second, weaker CETP inhibitor, dalcetrapib, increases HDL-C by 31–40%, without changing LDL-C. In the dal-OUTCOMES trial, dalcetrapib showed no benefit on cardiovascular outcomes [99]. The findings of the ILLUMINATE and dal-OUTCOMES trials have raised the issue of whether or not CETP inhibition is a viable approach to HDL-C raising. In addition, these trials also caused many clinicians to question whether the “HDL hypothesis” is physiologically important and relevant to cardiovascular medicine.

Two new CETP inhibitors (anacetrapib and evacetrapib) are in phase III clinical trials. Anacetrapib (MK-0859) raises HDL without affecting blood pressure [100]. The Determining Efficacy and Tolerability (DEFINE) trial randomized 1623 patients with coronary artery disease (CAD) with LDL-C < 100 mg/dl on statin therapy to 100 mg of anacetrapib or placebo [101]. Anacetrapib therapy

resulted in a 138% increase in HDL-C, a 40% reduction in LDL-C, and a 36% decrease in Lp[a]. The off-target effects seen with torcetrapib were not observed. Although DEFINE was not powered to test whether or not anacetrapib reduced risk for hard CAD related endpoints, there was a modest trend toward reducing risk for CAD related events, though this did not achieve statistical significance. The large REVEAL HPS-3/TIMI-55 trial will test the hypothesis that lipid modification with anacetrapib 100 mg daily reduces the risk of coronary death, myocardial infarction, or coronary revascularization in 30,000 patients with cardiovascular disease (CVD) or diabetes mellitus on optimal statin treatment with atorvastatin. The estimated study completion date is 2017 [102].

Evacetrapib is a benzazepine compound (LY248595) that is a potent and selective inhibitor of CETP both *in vitro* and *in vivo*. Clinical trials with evacetrapib showed substantially increased HDL-C (54–129%) and decreased LDL-C (14–36%) across a dose range of evacetrapib in 398 dyslipidemic patients [103]. Evacetrapib has shown no demonstrable effects on blood pressure or adrenal capacity to synthesize aldosterone or cortisol in preclinical studies. The effects of evacetrapib on cardiovascular outcomes are being examined in the Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes (ACCELERATE study), enrolling 11,000 patients after an acute coronary syndrome (ACS) [104].

Conclusion

Epidemiologic and observational studies consistently demonstrate that low levels of HDL-C increase risk for CHD and CHD-related events. Whether or not specific lipid modifying drugs provide benefit to patients with isolated low HDL-C or mixed dyslipidemia including low HDL-C largely relies on evidence derived from *post hoc* analyses of numerous clinical trials. Statins, fibrates, and niacin appear to exert benefit in patients with specific low HDL-C phenotypes. These findings await confirmation in prospective clinical trials. It is our opinion that many of the requisite confirmatory trials will not be performed. Therefore, the treatment recommendations noted herein with currently available drugs have significant limitations. By recognizing the importance of HDL functionality, new developments in lipid therapies may change the landscape of CHD prevention and treatment. It is hoped that newer pharmacologic approaches which raise serum HDL-C and HDL particle number in serum will help to lower residual risk for CV morbidity and mortality.

Practice points

A low serum HDL-C is among the most important risk factors for CAD.

Based on *post hoc* subgroup analyses from numerous trials, raising HDL-C appears to impact risk for acute cardiovascular events and contributes to slowing the rate of progression of atherosclerotic disease. However, HDL-C is not a target of therapy *per se*.

The following therapies can be considered in patients with low HDL-C irrespective of the amount of HDL-C raising observed:

- (A) Statin in the setting of low HDL-C with or without concomitant elevation in LDL-C;
- (B) Fibrate in patients with low HDL-C coupled with elevated triglycerides;
- (C) If a high risk patient has attained LDL-C < 70 mg/dL, non-HDL-C approximately 100 mg/dL, and apoB of 80 mg/dL with statin ± ezetimibe therapy, then adjuvant niacin therapy does not provide incremental benefit. However, if these patients have hypertriglyceridemia and low HDL-C, then niacin may provide incremental benefit based on AIM-HIGH.
- (D) Thiazolidinediones cannot be recommended at the present time to treat low HDL-C in patients with DM.

Research agenda

HDL particles are extremely complex; their proteome, lipidome, and cargo of microRNAs confer a diverse range of functionality.

The HDLs are a highly heterogeneous class of lipoproteins. It will be important to establish which fractions have greatest relevance to the antagonism of atherosclerosis.

It remains to be determined what relevance HDL functionality has to atherogenesis *in vivo* and how specific therapies and lifestyle modifications impact the capacity of HDL particles to antagonize endothelial dysfunction, reduce the oxidative and inflammatory tone of vascular walls (among other functions), and risk for CV events.

More prospective randomized studies are needed with both established drugs and emerging agents to better ascertain whether or not HDL-C raising or the modulation of HDL functionality provide reductions in risk for cardiovascular events.

The clinical relevance of dysfunctional HDL with impaired functionality and proatherogenic tendency is an area of intensive and urgent investigation.

References

- [1] Toth PP. High-density lipoprotein and cardiovascular disease. *Circulation* 2004;109:1809–12.
- *[2] Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012;380:572–80.
- *[3] Toth PP, Barter PJ, Rosenson RS, et al. High-density lipoproteins: a consensus statement from the National Lipid Association. *J Clin Lipidol* 2013;7(5):484–525.
- [4] Castelli WP, Doyle JT, Gordon T, et al. HDL cholesterol and other lipids in coronary heart disease. The cooperative lipoprotein phenotyping study. *Circulation* 1977;55:767–72.
- [5] Miller NE, Thelle DS, Forde OH, et al. The Tromsø heart-study. High-density lipoprotein and coronary heart disease: a prospective case-control study. *Lancet* 1977;1:965–8.
- [6] Assmann G, Cullen P, Schulte H. The Münster Heart Study (PROCAM). Results of follow-up at 8 years. *Eur Heart J* 1990;19(Suppl. A):A2–11.
- [7] Cooney MT, Dudina A, De Bacquer D, et al. SCORE investigators. HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk. *Atherosclerosis* 2009;206:611–6.
- [8] Walldius G, Jungner I, Holme I, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 2001;358:2026–33.
- [9] Frikke-Schmidt R, Nordestgaard BG, Stene MC, et al. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. *JAMA* 2008;299:2524–32.
- [10] Huxley RR, Barzi F, Lam TH, et al. Isolated low levels of high-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease. An individual participant data meta-analysis of 23 studies in the Asia-Pacific region. *Circulation* 2011;124:2056–64.
- *[11] Emerging Risk Factors Collaboration. Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 1993–2000;2009(302).
- [12] Jacobs DR, Mebane IL, Bangdiwala SI, et al. High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women, follow-up study of the Lipid Research Clinics Prevalence Study. *Am J Epidemiol* 1990;131:32–47.
- [13] Castelli WP. Cholesterol and lipids in the risk of coronary artery disease—the Framingham Heart Study. *Can J Cardiol* 1988;4:5A–10A.
- [14] Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol level. *JAMA* 1986;256:2835–8.
- [15] Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989;79:8–15.
- [16] Kitamura A, Iso H, Naito Y, et al. High-density lipoprotein cholesterol and premature coronary heart disease in urban Japanese men. *Circulation* 1994;89:2533–9.
- [17] Stampfer MJ, Sacks FM, Salvini S, et al. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med* 1991;325:373–81.
- [18] Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 2007;357(13):1301–10.
- [19] deGoma EM, Leeper NJ, Heidenreich PA. Clinical significance of high-density lipoprotein cholesterol in patients with low low-density lipoprotein cholesterol. *J Am Coll Cardiol* 2008;51:49–55.
- [20] Jafri H, Alsheikh-Ali AA, Karas RH. Meta-analysis: statin therapy does not alter the association between low levels of high-density lipoprotein cholesterol and increased cardiovascular risk. *Ann Intern Med* 2010;153:800–8.
- [21] Ridker PM, Genest J, Boekholdt SM, et al. HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. *Lancet* 2010;376:333–9.
- [22] Psaty BM, Anderson M, Kronmal RA, et al. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality, the Cardiovascular Health Study. *J Am Geriatr Soc* 2004;52(10):1639–47.

- [23] Sacco RL, Benson RT, Kargman DE, et al. High-density lipoprotein cholesterol and ischemic stroke in the elderly. The Northern Manhattan Stroke Study. *JAMA* 2001;285:2729–35.
- [24] Weverling-Rijnsburger AWE, Jonkers LJ, van Exel E, et al. High-density vs low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age. *Arch Intern Med* 2003;163:1549–54.
- [25] Corti MC, Guralnik JM, Salive ME, et al. HDL-C predicts coronary heart disease mortality in older persons. *JAMA* 1995;274:575–7.
- [26] Johnsen SH, Mathiesen EB, Fosse E, et al. Elevated high-density lipoprotein cholesterol levels are protective against plaque progression, a follow-up study of 1952 persons with carotid atherosclerosis the Tromso study. *Circulation* 2005;112(4):498–504.
- [27] Ishikawa K, Tani S, Watanabe I, et al. Effect of pravastatin on coronary plaque volume. *Am J Cardiol* 2003;92:975–7.
- [28] Wolfram RM, Brewer HB, Xue Z, et al. Impact of low high-density lipoproteins on in-hospital events and one-year clinical outcomes in patients with non-ST-elevation myocardial infarction acute coronary syndrome treated with drug-eluting stent implantation. *Am J Cardiol* 2006;98:711–7.
- [29] Foody JM, Ferdinand FD, Pearce GL, et al. HDL cholesterol level predicts survival in men after coronary artery bypass graft surgery: 20-year experience from the Cleveland Clinic Foundation. *Circulation* 2000;102. II90–4.
- [30] van der Steeg WA, Holme I, Boekholdt SM, et al. High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein a-I: significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies. *J Am Coll Cardiol* 2008;51:634–42.
- [31] Robins SJ, Lyass A, Zachariah JP, et al. Insulin resistance and the relationship of a dyslipidemia to coronary heart disease: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol* 2011;31:1208–14.
- [32] Toth PP, Potter D, Ming E. Prevalence of lipid abnormalities in the United States: The National Health and Nutrition Examination Survey 2003–2006. *J Clin Lipidol* 2012;6(4):325–30.
- [33] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356–9.
- [34] Ghandehari H, Kamal-Bahl S, Wong ND. Prevalence and extent of dyslipidemia and recommended lipid levels in US adults with and without cardiovascular comorbidities: the National Health and Nutrition Examination Survey 2003–2004. *Am Heart J* 2008;156:112–9.
- [35] Gatti A, Maranghi M, Bacchi S, et al. Poor glycemic control is an independent risk factor for low HDL cholesterol in patients with type 2 diabetes. *Diabetes Care* 2009;32:1550–2.
- [36] Morton J, Zoungas S, Li Q, et al. Low HDL cholesterol and the risk of diabetic nephropathy and retinopathy: results of the ADVANCE study. *Diabetes Care* 2012;35:2201–6.
- [37] Alsheikh-Ali AA, Lin JL, Abourjaily P, et al. Prevalence of low high-density lipoprotein cholesterol in patients with documented coronary heart disease or risk equivalent and controlled low-density lipoprotein cholesterol. *Am J Cardiol* 2007;100:1499–501.
- [38] Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003–2006. *Natl Health Stat Report* 2009;13:1–7.
- [39] Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. *Diabetes Care* 2009;32:287–94.
- [40] Bruckert E, Baccara-Dinet M, McCoy F, et al. High prevalence of low HDL-cholesterol in a pan-European survey of 8545 dyslipidaemic patients. *Curr Med Res Opin* 2005;21:1927–34.
- [41] Mahley RW, Pepin J, Palaoğlu KE, et al. Low levels of high-density lipoproteins in Turks, a population with elevated hepatic lipase. High-density lipoprotein characterization and gender-specific effects of apolipoprotein E genotype. *J Lipid Res* 2000;41:1290–301.
- [42] Vaisar T, Pennathur S, Green PS, et al. Shotgun proteomics implicates protease inhibition and complement activation in the anti-inflammatory properties of HDL. *J Clin Invest* 2007;117:746–56.
- [43] Toth PP. Reverse cholesterol transport: high-density lipoprotein's magnificent mile. *Curr Atheroscler Rep* 2003;5:386–93.
- [44] Toth PP. Activation of intracellular signaling systems by high-density lipoproteins. *J Clin Lipidol* 2010;4:376–81.
- [45] Nofer JR, Kehrel B, Fobker M, et al. HDL and arteriosclerosis: beyond reverse cholesterol transport. *Atherosclerosis* 2002;161:1–16.
- [46] Nofer JR, Walter M, Kehrel B, et al. HDL3-mediated inhibition of thrombin-induced platelet aggregation and fibrinogen binding occurs via decreased production of phosphoinositide-derived second messengers 1,2-diaclyglycerol and inositol 1,4,5-tris-phosphate. *Arterioscler Thromb Vasc Biol* 1998;18:861–9.
- [47] Toth PP. High-density lipoprotein: epidemiology, metabolism, and antiatherogenic effects. *Dis Mon* 2001;47:369–416.
- [48] Fryirs MA, Barter PJ, Appavoo M, et al. Effects of high-density lipoproteins on pancreatic beta-cell insulin secretion. *Arterioscler Thromb Vasc Biol* 2010;30:1642–8.
- *[49] Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 2011;364:127–35.
- [50] Yamamoto S, Yancey PG, Iikizler TA, et al. Dysfunctional high-density lipoprotein in patients on chronic hemodialysis. *J Am Coll Cardiol* 2012;60:2372–9.
- [51] Ansell BJ, Fonarow GC, Fogelman AM. High-density lipoprotein: is it always atheroprotective? *Curr Atheroscler Rep* 2006;8:405–11.
- [52] van de Woestijne AP, van der Graaf Y, Liem A-H, et al. Low HDL-cholesterol is not a risk factor for recurrent vascular events in patients with vascular disease on intensive lipid-lowering medication. *J Am Coll Cardiol* 2013. <http://dx.doi.org/10.1016/j.jacc.2013.04.101>.
- [53] Acharjee S, Boden WE, Hartigan PM, et al. Low levels of high density lipoprotein cholesterol and increased risk of cardiovascular events in stable ischemic heart disease patients: a post hoc analysis from the COURAGE trial. *J Am Coll Cardiol* 2013. <http://dx.doi.org/10.1016/j.jacc.2013.07.051>.
- [54] Briel M, Ferreira-Gonzalez I, You JJ, et al. Association between change in high-density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. *BMJ* 2009;338:b92.

- [55] Birjmohun RS, Hutten BA, Kastelein JJ, et al. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2005;45:185–97.
- [56] Lavigne PM, Karas RH. The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression. *J Am Coll Cardiol* 2013;61:440–6.
- [57] Nicholls SJ, Tuzcu EM, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007;297:499–508.
- [58] Ballantyne CM, Raichlen JS, Nicholls SJ, et al. Effect of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography: a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. *Circulation* 2008;117:2458–66.
- [59] Brown B, Zhao X, Cheung M. Should both HDL-C and LDL-C be targets for lipid therapy? A review of current evidence. *J Clin Lipidol* 2007;1:88–94.
- [60] Martin G, Duez H, Blanquart C, et al. Statin-induced inhibition of the Rho-signaling pathway activates PPAR- α and induces HDL apoA-I. *J Clin Invest* 2001;107:1423–32.
- [61] Schaefer EJ, Asztalos BF. The effects of statins on high-density lipoproteins. *Curr Atheroscler Rep* 2006;8:41–9.
- [62] Downs JR, Clearfield M, Weis S, et al. for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA* 1998;279:1615–22.
- *[63] Gotto Jr AM, Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation* 2000;101(5):477–84.
- [64] Packard CJ, Ford I, Robertson M, et al. for the PROSPER Study Group. Plasma lipoproteins and apolipoproteins as predictors of cardiovascular risk and treatment benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *Circulation* 2005;112(20):3058–65.
- [65] Ballantyne CM, Herd JA, Ferlic LL, et al. Influence of low HDL on progression of coronary artery disease and response to fluvastatin therapy. *Circulation* 1999;99(6):736–43.
- [66] Birjmohun RS, Hutten BA, Kastelein JJP, et al. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds. A meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2005;45:185–97.
- [67] Fruchart JC. Peroxisome proliferator-activated receptor- α activation and high-density lipoprotein metabolism. *Am J Cardiol* 2001;88(Suppl):24N–9N.
- [68] Ericsson C-G, Hamsten A, Nilsson J, et al. Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male post infarction patients. *Lancet* 1996;347:849–53.
- [69] Frick MH, S yv anne M, Nieminen MS, et al. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. *Circulation* 1997;96:2137–43.
- [70] Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular out-comes: a systematic review and meta-analysis. *Lancet* 2010;375:1875–84.
- [71] Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study, primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237–45.
- *[72] Rubins HB, Robins SJ, Collins D, et al. for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;341:410–8.
- *[73] Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation* 2000;102:21–7.
- [74] Tenenbaum A, Motro M, Fisman EZ, et al. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch Intern Med* 2005;165:1154–60.
- [75] Goldenberg I, Benderly M, Sidi R, et al. Relation of clinical benefit of raising high-density lipoprotein cholesterol to serum levels of low-density lipoprotein cholesterol in patients with coronary heart disease (from the Bezafibrate Infarction Prevention Trial). *Am J Cardiol* 2009;103:41–5.
- [76] Goldenberg I, Boyko V, Tennenbaum A, et al. Long-term benefit of high-density lipoprotein cholesterol-raising therapy with bezafibrate: 16-year mortality follow-up of the bezafibrate infarction prevention trial. *Arch Intern Med* 2009;169:508–14.
- [77] Scott R, O'Brien R, Fulcher G, et al. FIELD Study Investigators. Effects of fenofibrate treatment on cardiovascular disease in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care* 2009;32:493–8.
- *[78] ACCORD Study Group. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563–74.
- [79] Tunaru S, Kero J, Schaub A, et al. PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. *Nat Med* 2003;9:352–5.
- [80] Rubic T, Trottmann M, Lorenz RL. Stimulation of CD36 and the key effector of reverse cholesterol transport ATP binding cassette A1 in monocyte cells by niacin. *Biochem Pharmacol* 2004;67:411–9.
- [81] The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;231:360–81.
- [82] Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;323:1289–98.
- [83] Whitney EJ, Krasuski RA, Personius BE, et al. A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events. *Ann Intern Med* 2005;142:95–104.
- [84] Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583–92.
- [85] Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 2004;110:3512–7.

- [86] Taylor AJ, Lee HJ, Sullenberger LE. The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr Med Res Opin* 2006;22:2243–50.
- [87] Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 2009;361:2113–22.
- *[88] Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255–67.
- [89] <http://www.ctsu.ox.ac.uk/~thrive/>.
- [90] Murthy S, Born E, Mathur SN, et al. Liver-X-receptor-mediated increase in ATP-binding cassette transporter A1 expression is attenuated by fatty acids in CaCo-2 cells: effect on cholesterol efflux to high-density lipoprotein. *Biochem J* 2004;377:545–52.
- [91] Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005;28:1547–54.
- [92] van Wijk JP, de Koning EJ, Martens EP, et al. Thiazolidinediones and blood lipids in type 2 diabetes. *Arterioscler Thromb Vasc Biol* 2003;23:1744–9.
- [93] Mazzone T, Meyer PM, Feinstein SB. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2007;296:2572–81.
- [94] Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA* 2008;299:1561–73.
- [95] Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitazone clinical trial in MacroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279–89.
- [96] Barter PJ, Caulfield M, Eriksson M, et al. ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;357:2109–22.
- [97] Kastelein JJ, van Leuven SI, Burgess L, et al. RADIANCE 1 Investigators. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med* 2007;356:1620–30.
- [98] Bots ML, Visseren FL, Evans GW, et al. RADIANCE 2 Investigators. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double blind trial. *Lancet* 2007;370:153–60.
- [99] Schwartz GG, Olsson AG, Abt M, et al. dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;367:2089–99.
- [100] Krishna R, Anderson MS, Bergman AJ, et al. Effect of the cholesteryl ester transfer protein inhibitor, anacetrapib, on lipoproteins in patients with dyslipidaemia and on 24-h ambulatory blood pressure in healthy individuals: two doubleblind, randomised placebo-controlled phase I studies. *Lancet* 2007;370:1907–14.
- *[101] Cannon CP, Shah S, Dansky HM, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* 2010;363:2406–15.
- [102] [Clinical trial.gov](http://clinicaltrials.gov). REVEAL: randomized evaluation of the effects of anacetrapib through Lipid-modification. <http://clinicaltrials.gov/ct2/show/NCT01252953>; 2010.
- [103] Nicholls SJ, Brewer HB, Kastelein JJ, et al. Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. *JAMA* 2011;306:2099–109.
- [104] <http://clinicaltrials.gov/show/NCT01687998>.