

Apolipoprotein A-I and Risk for Cardiovascular Diseases

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Increased concentrations of high-density lipoprotein (HDL) cholesterol have been closely associated with decreased risk of future cardiovascular disease. This protective effect of HDL has been mainly attributed to its involvement in reverse cholesterol transport. More recently, it has been suggested that apolipoprotein A-I (apoA-I), the major protein component of HDL, possesses nearly identical information as HDL in terms of risk prediction for future cardiovascular disease. This makes apoA-I a very attractive biomarker candidate for implementation into clinical practice, taking into account its analytical advantages. This review summarizes our current knowledge based on observations from recent studies, with emphasis on potential pathophysiological mechanisms of action and on the clinical utility of apoA-I as a predictor of cardiovascular risk.

Introduction

The inverse relationship between high-density lipoprotein (HDL) cholesterol and risk of cardiovascular disease (CVD) is well recognized, establishing low HDL cholesterol levels as a strong and independent marker of clinical outcome. Indeed, within the Framingham study [1], HDL cholesterol was the most potent predictor of coronary risk over 12 years of follow-up in multivariable analyses. More importantly, HDL cholesterol was able to predict coronary heart disease (CHD) risk even if total cholesterol was normal or near normal (Fig. 1) [2]. In addition, it has been shown that each 1-mg/dL decrease in HDL cholesterol resulted in an increase in the risk for CHD by 2% in men and 3% in women [3].

Atheroprotective properties of HDL cholesterol have been mainly attributed to its ability to transfer cholesterol excess from peripheral cells to the liver, a process known as reverse cholesterol transport (RCT). However, HDL also

possesses pleiotropic effects (ie, anti-inflammatory, antioxidant, and antithrombotic) properties that are considered to be antiatherogenic [4,5]. Numerous investigations during recent years have suggested that apolipoprotein A1 (apoA-I) might represent an important predictor of HDL cholesterol levels in the bloodstream because it is the major apolipoprotein constituent of HDL cholesterol. ApoA-I plays a prominent role in HDL metabolism as a primary acceptor of unesterified cholesterol from the peripheral tissues. This article briefly reviews the role of apoA-I in RCT and further focuses on the potential clinical utility of apoA-I in assessing risk of future CVD.

Structure of ApoA-I

ApoA-I is the most abundant protein within HDL, comprising around 70% of its total protein mass. This apolipoprotein represents a 243-amino acid polypeptide, which is mainly synthesized by the liver and intestine, with a molecular mass of 28 kDa. However, apoA-I might also be released during intravascular lipolysis of triglyceride (TG)-rich lipoproteins by lipoprotein lipase (LPL), as well as a result of remodeling of mature, spherical HDL by phospholipid transfer protein (PLTP), cholesteryl ester transfer protein (CETP), and hepatic lipase (HL) [6•]. Newly secreted apoA-I should be large enough to avoid its filtration through renal glomeruli and endocytosis by the cubilin/megalin receptors in the proximal renal tube. ApoA-I is present in plasma in three different forms. Five to ten percent of human apoA-I exists as a monomolecular form either in a lipid-unassociated state or as partially lipidated, containing only trace amounts of lipids. The second form is a component of nascent, discoidal HDL, which contains no core but two or three molecules of apoA-I in a complex with phospholipids. Finally, approximately 90% of apoA-I exists as part of mature, spherical HDL particles.

Reverse Cholesterol Transport

The main mechanism for the atheroprotective effect of HDL is thought to be RCT [7], a process whereby HDL delivers excess cholesterol from peripheral tissue to the liver to either be recycled or excreted from the body directly, or after conversion to bile acids. Mono-

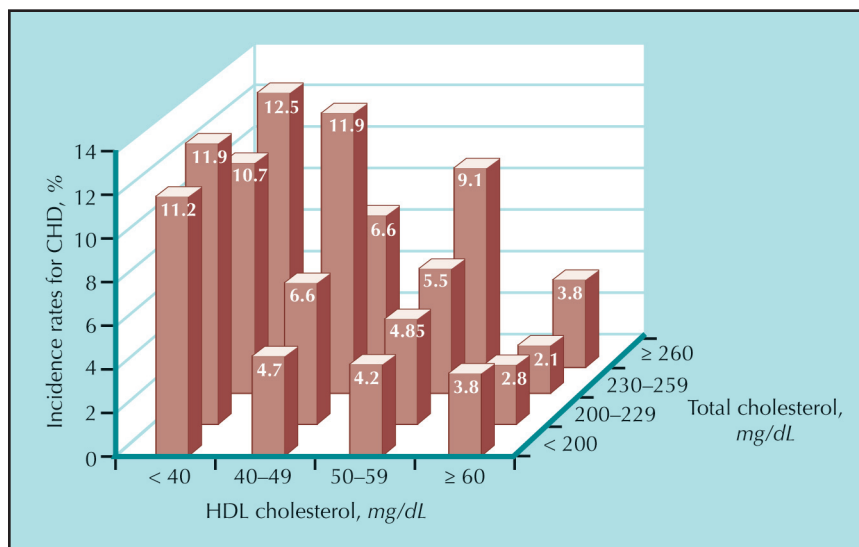


Figure 1. High-density lipoprotein (HDL) cholesterol predicts incident coronary heart disease (CHD) independently of total cholesterol levels. (Adapted from Castelli et al. [2].)

molecular lipid-poor or lipid-free apoA-I represents a primary ligand for the adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) [8]. ABCA1 is a regulatory protein that facilitates the energy-dependent translocation of cholesterol from the inner leaflets of cell membranes to the extracellular space, thereby promoting cellular cholesterol efflux, an initial step in RCT. Upon binding to ABCA1, apoA-I rapidly acquires phospholipids and unesterified cholesterol from peripheral cells to be converted into nascent, disc-shaped HDL. Furthermore, apoA-I mediates the activation of the enzyme lecithin:cholesterol acyltransferase (LCAT), which esterifies the free cholesterol content of discoidal HDL, thus providing HDL with a core of cholesteryl esters (CE). LCAT-mediated esterification of nascent HDL also results in structural changes within HDL (ie, they are expanding and converting from discoidal to spheroidal, mature HDL). CEs are further transported by HDL through two main pathways: via direct delivery to the liver and subsequent “selective lipid uptake,” mediated by scavenger receptor-B1 (SR-B1) for excretion in bile or for recycling, or through the interaction with CETP, which transfers CE from HDL to apoB-containing particles (in exchange for triglycerides) and then returns them to the tissue (including the liver) via LDL receptors.

ApoA-I in CHD Risk Assessment

Although the inverse relationship between HDL cholesterol concentrations and risk of future CHD is well recognized and HDL cholesterol has been incorporated into various algorithms for calculating CVD risk, several studies have recently demonstrated that apoA-I might provide almost identical prognostic information as HDL, but several studies have suggested that apoA-I might even improve our ability to identify patients at risk for future CHD [9].

Secondary prevention studies

To date, a number of studies have examined the value of apoA-I in subjects with CHD [9]. Initial evidence on the prognostic role of apoA-I dates back to the early 1980s and was based on the results of a small case-control study that included only 83 patients with clinically stable CHD and 25 healthy control subjects. The results showed that apoA-I is a more powerful predictor of CHD than HDL cholesterol alone [10]. Since then, results from numerous prospective studies conducted in patients with manifest CHD demonstrated an independent inverse association between apoA-I concentrations and future cardiovascular events.

Moss et al. [11] investigated the predictive value of several hemostatic and lipid biomarkers on the risk of recurrent coronary events in 1045 patients who were recruited 2 months after an acute myocardial infarction (MI) and were followed for 4 years. In multivariate survival analysis, in contrast to low HDL cholesterol, low apoA-I levels remained a significant predictor of recurrent coronary events. Furthermore, Bolibar et al. [12] found an independent association between decreased levels of both HDL as well as apoA-I and the subsequent incidence of MI in 3000 patients with angina pectoris from the European Concerted Action on Thrombosis and Disabilities (ECAT) study who were followed for 2 years. Similar prognostic information was found for both markers, with a relative risk (RR) per 1 SD increase in HDL cholesterol concentration of 0.68 (95% CI, 0.55–0.84) and 0.66 (95% CI, 0.54–0.81) for apoA-I. Finally, results from the more recent AtheroGene study by Schlitt et al. [13], conducted in 1298 patients with angiographically confirmed CHD, showed that increased concentrations of apoA-I at baseline were associated with decreased risk of future fatal and nonfatal cardiovascular events during a 3.9-year follow-up period, and this association was independent of a variety of potential confounders (hazard rate ratio [HRR] of 0.41; 95% CI, 0.22–0.79 for quartile 4 vs quartile 1), whereas HDL in

this study was not related to the combined endpoint. Such association held true even when the prognostic value of decreased apoA-I on subsequent cardiovascular events was assessed separately in patients on statin therapy.

Primary prevention studies

More than 20 long-term prospective studies have been published so far, assessing, among others, the association between apoA-I concentration and risk of future CHD in apparently healthy subjects from the general population [14••]. However, in the primary prevention setting, the strength of the association between low apoA-I and risk of subsequent CHD seems to be less consistent than has been observed in studies conducted in patients with CHD. Evidence from early prospective studies has demonstrated a rather low predictive value of apoA-I, whereas several more recent investigations suggested that apoA-I might represent a better risk predictor than HDL.

For instance, in a nested case-control study conducted within the Physicians' Health Study (a cohort of initially healthy men aged 40 to 84 years), it has been found that apoA-I did not add significantly to risk prediction in a multivariate model that included the total cholesterol/HDL cholesterol ratio [15]. In the Quebec Cardiovascular Study [16], among 2155 middle-aged men with 116 fatal/nonfatal coronary events during a 5-year follow-up period, adjustment for several lipid variables resulted in a loss of the association between apoA-I and disease risk. Likewise, in the Atherosclerosis Risk in Communities (ARIC) study [17], which included 12,339 initially healthy individuals of whom 725 subjects developed an incident CHD event over 10 years of follow-up, apoA-I was a strong predictor when considered alone but was no longer predictive when considered together with LDL, HDL, and TGs [17]. The recently published Northwick Park Heart Study [18], conducted in 2508 men aged 50 to 61 years with no signs of CHD at baseline who were followed for 6 years, also found no statistically significant association between apoA-I and CHD risk in multivariable analysis. However, in this study, the ratio of apoB/apoA-I was associated with the strongest effect on future CVD risk.

We also assessed the value of apoA-I for the prediction of future coronary events in both genders within the Monitoring of Trends and Determinants in Cardiovascular Disease/Kooperative Gesundheitsforschung in der Region Augsburg (MONICA/KORA Augsburg) study [19], comprising 1414 men and 1436 women aged 35 to 64 years without a prior coronary event at baseline. In total, 114 incident coronary events among men and 31 events among women were registered during a follow-up period of 13 years. Although an increment of 1 SD in the serum concentration of apoA-I tended to be associated with a decreased risk of coronary events in both sexes (men had a HR of 0.89; 95% CI, 0.73–1.08; and women had a HR of 0.82; 95% CI, 0.55–1.21), this did not reach statistical

significance in a fully adjusted model, resulting in a HR of 0.91 (95% CI, 0.75–1.12) and 0.91 (95% CI, 0.62–1.32) for men and women, respectively. In this study, however, HDL cholesterol among women also lost its significance after multivariable adjustment, whereas apoB was a strong predictor in both sexes.

Within the Prospective Epidemiological Study of Myocardial Infarction (PRIME) trial [20], the predictive ability of various HDL particles such as HDL cholesterol, apoA-I, LpA-I, and LpA-I/LpA-II was evaluated in a cohort of 9073 men, among whom 289 subjects experienced at least one CHD event over a 5-year follow-up period. Low apoA-I was found to be the strongest predictor of incident CHD, even more powerful than HDL cholesterol (RR for apoA-I was 0.39; 95% CI, 0.26–0.58) for quintile 1 versus quintile 5 and for HDL cholesterol the RR was 0.57 (95% CI, 0.38–0.86).

However, the strongest evidence in support of a prognostic value of apoA-I came from the Apolipoprotein-related Mortality Risk (AMORIS) study [21••], representing a large cohort ($n = 175,553$) of Swedish men and women followed for an average of 5.5 years. During this period, 864 men and 359 women suffered from a fatal MI. Again, in univariate analysis, the RR for a fatal MI for both sexes decreased to 0.5 in the top quartile compared with the bottom quartile of the apoA-I distribution, and the magnitude of this association was comparable with that obtained for HDL cholesterol. Moreover, apoA-I retained its strong predictive power even when added to a model including total cholesterol and TG. Similar results could be shown in individuals aged 70 years or older. In contrast, the predictive power of conventional lipid measures was weaker or even disappeared in this age group.

More recently, the prognostic utility of HDL cholesterol and apoA-I have been compared head to head in the Women's Health Study, a large cohort of middle-aged normocholesterolemic women who were followed for 10 years for the occurrence of subsequent cardiovascular events [22]. In multivariable analysis, subjects in the top quintile of apoA-I distribution demonstrated a significantly decreased risk for future cardiovascular events compared with those in the bottom quintile (RR of 0.57; 95% CI, 0.42–0.77). The effect of increased concentrations of HDL cholesterol on incident CVD was slightly more pronounced than that of apoA-I, revealing a RR of 0.43 (95% CI, 0.30–0.61 for quintile 5 vs quintile 1).

Thus, considering the growing literature on the predictive value of apoA-I in CVD, a formal meta-analysis is needed to provide unbiased information on the association between apoA-I and disease outcome. Indeed, a meta-analysis including 21 eligible studies with a total number of 6333 CHD cases was recently reported by Thompson et al. [14••]. It confirmed a significant and independent association between decreased apoA-I concentrations and future risk of CHD, resulting in a combined RR of 1.62 (95% CI, 1.43–1.83) (Fig. 2).

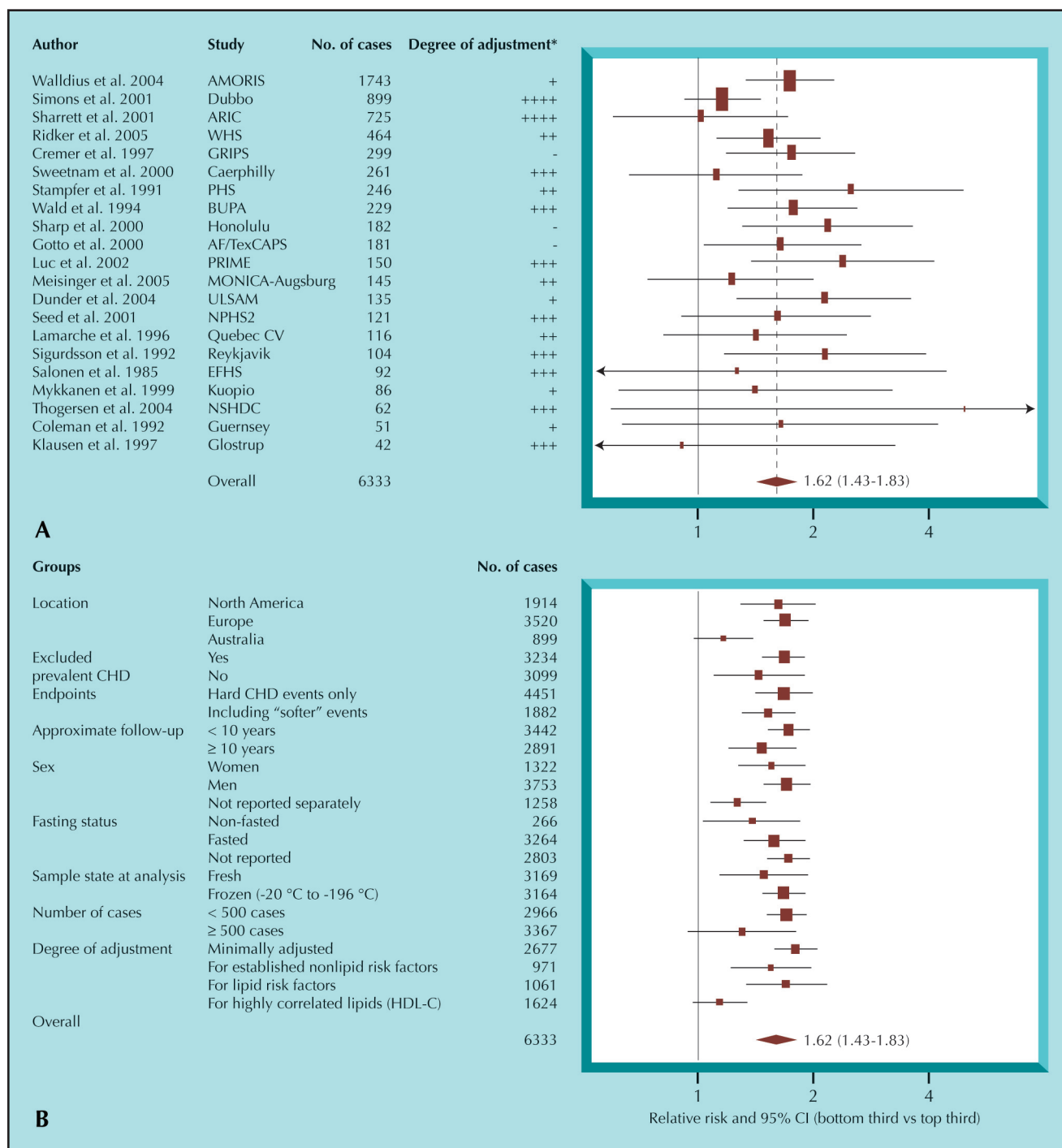


Figure 2. Reported associations between baseline levels of apolipoprotein A-I and risk of coronary heart disease (CHD) in prospective studies in essentially general populations (**A**) and grouped by various study characteristics (**B**). Asterisk indicates reported degree of adjustment. Minus symbol indicates no adjustment; + symbol indicates minimal (eg, age, sex) adjustment; ++ symbol indicates adjustment for established nonlipid risk factors; +++ indicates adjustment for lipid risk factors; and ++++ indicates adjustment for highly correlated lipids. HDL-C—high-density lipoprotein cholesterol. (Adapted from Thompson and Danesh [14••]; with permission.)

Risk prediction of apoA-I in patients on lipid-lowering medication

ApoA-I has also been found to be a potent predictor of CVD risk in the situation when conventional lipid measures often lose their prognostic value, namely during lipid-lowering interventions.

In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) clinical trial [23], which used lovastatin for primary prevention in a low-risk population for CHD ($n = 6605$), apoA-I measured at baseline was able to significantly predict risk of major acute coronary events. More importantly, only “on-treatment”

Table 1. Effects and mechanisms of current and emerging drugs that target HDL and ApoA-I

Drug	Clinical effects on HDL cholesterol	Mechanisms
Current therapies		
Nicotinic acid	Increase 15%–35%	Decrease hepatic A-I catabolism; decrease holoparticle uptake (β -chain ATP synthase)
Fibrates	Increase 5%–15%	PPAR α agonism: increase hepatic A-I synthesis, A-I mRNA synthesis, and A-I mRNA stability
Statins	Increase 5%–10%	Increase hepatic A-I synthesis and mRNA synthesis
Thiazolidinediones	Increase 10%–20%	Increase hepatic A-I synthesis and possible PPAR α activation
Emerging therapies		
ApoA-I Milano (ETC-216)	No sustained HDL cholesterol response	Mimics beneficial effects of apoA- I
ApoA I mimetics (D4-F)	Untested in humans	Mimics beneficial effects of apoA- I
CETP inhibitors		
JTT-705	Increase 30%–40%	Inhibits the transfer of CE from HDL to apoB lipoproteins
Torcetrapib	Increase 50%–100%	Inhibits the transfer of CE from HDL to apoB lipoproteins

ApoA-I—apolipoprotein A-I; ATP—adenosine triphosphate; CE—cholesteryl ester; CETP—cholesteryl ester transfer protein; HDL—high-density lipoprotein; PPAR α —peroxisome proliferator-activated receptor α .
(Adapted from Meyers and Kashyap [32•].)

apoA-I achieved statistical significance as a prognostic marker of outcome after 1 year, whereas HDL cholesterol was not related to cardiovascular event reduction.

A total of 9014 patients with a previous history of CHD were randomized to receive pravastatin or placebo within the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study [24], a secondary prevention trial. In the placebo group, baseline apoA-I concentrations were a better prognostic marker of subsequent CHD events over 6 years than HDL cholesterol, with a HR of 0.41 (95% CI, 0.24–0.69) and 0.52 (95% CI, 0.33–0.82), respectively, for each change in lipid level. Moreover, after 12 months of treatment with pravastatin, HDL cholesterol lost its predictive power, whereas apoA-I concentrations remained statistically significantly associated with coronary risk (HR of 0.49; 95% CI, 0.26–0.92) for every gram per liter increase in apoA-I level.

In a smaller secondary prevention trial with lipid-lowering therapy (statin therapy either alone or in combination with cholestyramine or gemfibrozil), van Lennep et al. [25] studied 848 patients with angiographically proven CHD. Again, on-treatment level of apoA-I was the most significant predictor of major events (MI and all-cause mortality) for both sexes, whereas a predictive value of HDL cholesterol was seen in women only.

Finally, the association between apoA-I concentrations and future cardiovascular events has also been investigated in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial [26], a trial of pravastatin use in an older population of 5804 subjects. In multivariate analysis, a 1-SD increase in apoA-I con-

centration was inversely associated with the primary endpoint (CHD death, nonfatal MI, and fatal/nonfatal stroke) over 3.2 years of follow-up. However, this association reached a formal level of statistical significance only in the placebo group, resulting in a HR of 0.72 (95% CI, 0.60–0.86), whereas in the pravastatin group apoA-I was not significantly related to future CVD risk (HR of 0.89; 95% CI, 0.73–1.09).

ApoA-I and Cerebrovascular Risk

Again, data from the Apolipoprotein-related Mortality Risk (AMORIS) study [27] further demonstrated that increased apoA-I concentrations were significantly associated with a decreased risk of stroke ($n = 1111$ cases). For a 1-SD increase in apoA-I, the age- and gender-adjusted RR was 0.84 (95% CI, 0.79–0.89), which was similar to values obtained for HDL cholesterol with a RR of 0.81 (95% CI, 0.77–0.86).

These findings, however, are in contrast with data from the Atherosclerosis Risk in Communities (ARIC) study cohort [28], in which the relationship between circulating lipoproteins and the incidence of ischemic stroke was studied in 14,175 middle-aged men and women with 305 case-subjects during 10 years of follow-up. The HR of ischemic stroke for individuals in the top quartile of apoA-I was 0.91 (95% CI, 0.64–1.31) compared with the referent quartile after taking into account other confounders, including traditional risk factors, diabetes, and hemostatic markers. Similarly, HDL cholesterol concentrations did not predict risk of stroke in this population.

Measurement Issues of ApoA-I

Thus, given that the prognostic power of apoA-I in CVD risk assessment is almost identical to that of HDL cholesterol or even superior, it has been suggested that it might represent a reliable alternative to measurement of HDL cholesterol in routine clinical practice [29•]. The analytical performance of apoA-I measurement has several potential advantages compared with HDL cholesterol, which could facilitate the implementation of apoA-I in the clinic. Indeed, apoA-I can be measured directly by fully automated immunonephelometric and immunoturbidimetric assays, using specific antibodies in the liquid phase, and these measurements can be carried out even in non-fasting blood samples. In addition, apoA-I measurement procedures are commercially available, and in contrast to HDL cholesterol, are standardized and widely internationally validated by the use of WHO/IFCC International Reference Material SP1-01. It has been also demonstrated that coefficients of variation for apoA-I measurements are very low and vary between 2.1% and 5.6% [30], thereby indicating excellent precision and comparability of this laboratory procedure.

Currently Available Therapies to Raise HDL Cholesterol

Taking into account the antiatherogenic properties of HDL cholesterol, and apoA-I in particular, these lipoproteins might represent a perfect therapeutic target. Because pharmacologic interventions aimed at increasing these lipoproteins could be accomplished through the various routes of the RCT pathway, numerous therapeutic compounds are currently available that 1) raise HDL cholesterol levels either by affecting cholesterol efflux or by increasing formation of or decreasing the catabolism of HDL and its defined functional proteins; or 2) mimic the antiatherogenic effects of HDL and apoA-I (Table 1).

Among common therapeutic agents, only four (statins, fibrates, nicotinic acid, and thiazolidinediones [TZDs], as monotherapy or in combination) have been shown to raise HDL cholesterol. Moreover, a number of randomized clinical trials have conclusively demonstrated a significant benefit of therapy to increase HDL on cardiovascular outcome. These studies, however, are not discussed here in detail as they were the subject of several excellent recent reviews [31,32•]. However, several mechanisms of action of these drugs are discussed here.

The mechanism through which statins increase HDL levels by 5% to 10% is not entirely clear. It has been suggested that statin-induced increase in HDL cholesterol could be related to the reduction of CETP levels, thereby preventing further catabolism of HDL and returning it to circulation [33]. Moreover, statins could also inhibit the Rho-signaling pathway, which results in the induction of peroxisome proliferator-activated receptor α (PPAR α) with a subsequent transcription of apoA-I [34,35].

Fibric acid derivatives, or fibrates, being a class of compounds with an agonistic action for PPAR α , result in a 10% to 20% increase in HDL cholesterol. PPAR α represents a well-known subfamily of nuclear receptors that act as transcription factors [36]. After activation, PPAR α binds to its response elements, thereby initiating the transcription of several genes such as *ApoA-I*, *SR-B1*, and *ABCA1*, which are directly involved in RCT. Consequences of this interaction are enhanced hepatic secretion of apoA-I, acceleration of cholesterol efflux from peripheral cells due to upregulation of ABCA1, and increased uptake of HDL cholesterol by the liver due to stimulation of SR-B1 expression.

TZDs, which possess potent PPAR α agonistic activity, show only moderate HDL-increasing effects of around 15%, usually in diabetic patients and in patients with other metabolic disorders [37,38]. Some investigators have linked these properties of TZDs to partial agonism with PPAR α , whereas others have shown stimulation of LXR by TZDs that further lead to upregulation of *ABCA1* gene expression [39].

Among all established therapeutic agents currently used in clinical practice for raising HDL cholesterol, however, nicotinic acid has the most pronounced effects, especially in subjects with isolated low HDL cholesterol. This increase in HDL cholesterol, nevertheless, does not exceed 30% to 35%. The mechanism by which nicotinic acid enhances HDL cholesterol concentration consists of a decreased functional catabolic rate of apoA-I due to inhibition of its hepatic uptake, and also due to its ability to decrease hepatic lipase activity [40].

Emerging Therapies to Raise HDL/ApoA-I

Despite all efforts, currently available medications commonly used in clinical practice raise HDL cholesterol only up to 35%, even in patients on combinations of various lipid-lowering medications (eg, statins and nicotinic acid). This has prompted investigators to search for novel compounds to elevate HDL cholesterol [41].

ApoA-I Milano

Very recently, growing interest has focused on ApoA-I Milano, a naturally occurring mutant form of ApoA-I characterized by a single amino acid substitution at position 173 where arginine is replaced by cysteine. ApoA-I Milano was initially discovered in the early 1980s in northern Italy as a point mutation, and individuals who carry this genetic defect are characterized by very low HDL cholesterol but without increased risk of atherosclerosis [42]. This paradox could possibly be explained by the powerful antioxidant activity of apoA-I Milano that is several times higher than that of wild-type apoA-I and by its increased capacity to transfer cholesterol from peripheral tissues to the liver [43••]. Potent antiatherogenic activities of apoA-I Milano have been recently demonstrated in patients with acute coronary syndromes.

Nissen et al. [44•] reported that intravenous recombinant apoA-I Milano-phospholipid complexes (ETC-216) given at weekly intervals resulted in a statistically significant reduction in atheroma burden (4.2% reduction in the volume of coronary atheroma as measured by intravascular ultrasound). These investigators have further demonstrated that regression of atherosclerotic plaque was mainly due to concomitant reduction of the external elastic membrane area, with no changes in lumen volume [45]. Thus, apoA-I Milano might represent a very powerful therapeutic agent for the treatment of CVD. However, these results clearly require confirmation in larger trials with clinical endpoints. A limitation of this approach obviously consists in the intravenous infusion of ETC-216, which reduces its long-term clinical applicability.

ApoA-I mimetics

The search for an orally active apoA-I mimetic resulted in the discovery of D-4F, an 18 D-amino acid peptide that has no sequence homology with apoA-I but forms a class A amphipathic helix, thereby mimicking the lipid-binding properties of apoA-I [46]. In experimental animal models, D-4F, given orally, has been shown to prevent lesion formation in young mice [47], and in combination with pravastatin caused existing lesion to regress in old mice [48]. It has further been demonstrated that D-4F might inhibit inflammation and thrombus formation as well as reduce the association of myeloperoxidase with apoA-I in vivo [46]. However, no studies so far have been carried out in humans and, therefore, no definite statement can be made regarding its clinical utility and safety.

Inhibition of CETP

Inhibition of the transfer of cholesterol from HDL to VLDL/LDL fractions by CETP could represent another mechanism for raising HDL concentration [49]. Experimental studies have demonstrated that JTT-705, a chemical inhibitor of CETP (thioester), promotes cholesterol ester efflux from macrophages and increases large HDL2 particles [49]. When taken by humans in phase II trials, JTT-705 led to reduced CETP activity of 36% and significantly increased HDL cholesterol concentration by 34% [50]. A second new oral CETP inhibitor, torcetrapib, investigated in a small phase II placebo-controlled trial, profoundly increased HDL cholesterol by as much as 106% when given at a dose of 120 mg twice daily for 4 weeks [51]. However, several mechanistic effects of this intervention are unclear, and large clinical trials are needed to establish the role of torcetrapib in clinical practice. In particular, a combination of this compound with a statin could offer large clinical benefit.

Conclusions

The pivotal role of LDL cholesterol for the development of atherosclerosis and its clinical complications has been

unequivocally established, and lowering of LDL cholesterol carries important clinical benefit in secondary and in primary prevention. However, all major trials have shown a relative risk reduction of approximately 30%, leaving a considerable fraction of the population at continuing increased risk. Consequently, interest has focused on HDL cholesterol to improve risk prediction and also as a target for intervention. However, to date the measurement of HDL cholesterol is hampered by several methodologic shortcomings that might be overcome by the measurement of apoA-I. The currently available large database shows that low apoA-I levels are at least as predictive as low HDL cholesterol for CVD, and several compounds to address this target are also being tested at present.

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