HDL-c is a powerful lipid predictor of cardiovascular diseases

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SUMMARY

Relationship between HDL-c and cardiovascular diseases: Beyond the role of low-density lipoprotein cholesterol (LDL-c) in the development of atherosclerosis, growing evidence suggest that high-density lipoprotein cholesterol (HDL-c) is a powerful predictor of cardiovascular disease. Indeed, epidemiological, mechanistic and intervention studies suggest that low HDL-c is a major cardiovascular risk factor and that increasing HDL-c plasma levels may be beneficial, particularly in patients with low HDL-c levels. The inverse association between HDL-c concentrations and cardiovascular risk is continuous without threshold value. Thus, any categorical definition of low HDL-c is arbitrary. Protective effects of HDL: HDL particles are highly heterogeneous in structure and intravascular metabolism. Antiatherogenic properties of HDL include its role in the reverse cholesterol transfer, besides its antioxidant, anti-inflammatory and antiapoptotic activities. What should clinicians do?: From a practical point of view, HDL-c should be systematically measured to assess the cardiovascular risk in patients. The first step to consider in subjects with low HDL-c is to look for specific causes and give advice to change inappropriate lifestyle components associated with low HDL-c, such as smoking, lack of physical exercise and overweight. Patients with very low HDL-c need a thorough evaluation by specialist physicians. Statins are associated with a modest increase of HDL-c (5%) while fibrates and nicotinic acid increase HDL-c by 10% and 20% respectively.

Introduction

High serum levels of low-density lipoprotein cholesterol (LDL-c) constitute a major risk factor for premature development of coronary heart disease (CHD) (1,2). Complementing the clinical and epidemiological studies assessing the role of LDL-c, it was subsequently demonstrated that decreasing LDL-c levels with statin has a major impact on cardiovascular disease (3). The so-called lower-the-better hypothesis is no longer valid as a recent meta analysis convincingly demonstrated that achieving low LDL-c brings additional benefit for patient at high cardiovascular risk (4).

However, a substantial body of evidence derived from epidemiological studies, clinical data and intervention trials also shows that low serum levels of cholesterol transported by high-density lipoproteins (HDL-c) are powerful lipid predictor of cardiovascular disease. One-third of dyslipidaemic patients treated with statin displays low HDL-c levels (Figure 1) (5). In addition, hypoHDLemia is a frequent condition in patients with cardiovascular disease. Thus treatment aiming at increasing HDL-c levels may bring additional benefit in a large number of patients presenting hypoHDLemia (6).

Despite the importance of HDL-c in the transport of cholesterol, hypo- and hyperHDLemias were disregarded in the WHO classification of dyslipidaemias. The relatively late emergence of this lipoprotein as a key factor protecting against atherosclerosis and cardiovascular disease is explained by the close association of HDL-c with other risk factors including abnormal LDL pattern and hypertriglyceridemia, the complexity of HDL metabolism and by the absence of drugs which specifically increase HDL-c levels without affecting triglyceride levels. In addition the mechanisms by which HDL particles might decrease the burden of cardiovascular disease is still not well understood and by no mean multifactorial.
Metabolism of HDL and its antiatherogenic functions

Spherical plasma HDL are generated by intravascular processes from lipid poor particles produced by the liver or intestine and also released from lipolysis of triglyceride-rich lipoproteins. Initial lipidation of these lipid-poor particles occurs at cellular membrane via the ABCA1-mediated efflux of cholesterol and phospholipids. Subsequently, esterification of cholesterol by LCAT (lecithin cholesterol acyltransferase) generates larger particles (HDL-2). These large lipoproteins can be converted into smaller HDL-3 particles by cholesterol ester transfer protein (CETP), which exchanges cholesterol and triglyceride with VLDL. HDL particles can be taken up by the liver or HDL lipids can also be catabolised separately from apolipoprotein and undergo selective uptake by the liver.

Beside reverse cholesterol transfer of cholesterol from peripheral cells to the liver, HDL particles possesses multiple antiatherogenic activities including antioxidative, anti-inflammatory, antiapoptotic, anti-thrombotic and vasodilatory properties. Antioxidative activity is related to paroxonase, platelet-activating factor acetyl hydrolase (PAH-AH) and LCAT. When HDL particles lose their normal biological activities they become dysfunctional. However, the relative part of dysfunctionality and reverse cholesterol transport activity in the protection of vascular wall remains indeterminate. Anti-inflammatory activity is illustrated by the ability to inhibit adhesion molecule expression and IL-6 production in endothelial cells exposed to TNF-alpha.

Epidemiological evidence

HDL-c levels predict coronary heart disease

The landmark epidemiological study which identified low HDL-c levels as independent risk factor for CHD is the Framingham Heart study. In this prospective study, HDL-c was measured from 1969 to 1971 in men and women 50 years of age and older. The inverse relationship between HDL-c levels and myocardial infarction was found to be even stronger in women when compared with men (7). Interestingly, recent analyses of HDL subpopulations were carried out in the Framingham offspring study. Indeed, HDL particles are highly heterogeneous in structure, intravascular metabolism and antiatherogenic activity. Large alpha-1 HDL particles were most significantly associated with CHD prevalence (8). However, we should acknowledge that there are no subpopulations of HDL which can be routinely measured and might give a better evaluation of the cardiovascular risk. Indeed, many studies which measure HDL-2 and HDL-3 as well as LpA1, LpA1–A2 were not able to consistently find a better marker for cardiovascular disease.

This inverse relationship between HDL-c and CHD risk was also demonstrated in the PROCAM study. Men with HDL-c levels < 0.90 mmol/l had a fourfold increased risk of CHD over a 6-year period.
compared to men with HDL-c levels ≥ 0.90 mmol/l (9). A significant association between low HDL-c and increased risk of CHD remained even after adjustment for other risk factors.

An analysis of four prospective studies (Framingham Study, Lipid Research Clinics Prevalence Mortality Follow-up Study, Coronary Primary Prevention Trial and Multiple Risk Factor Intervention Trial) showed that a 1% decrease in plasma levels of HDL-c was associated with a 2–3% increase in the risk of CHD. The finding was consistent across the studies and was independent of other risk factors, including plasma LDL-c (10).

The finding that HDL-c is a major risk factor was confirmed in Israel (11) and Asian countries in which cardiovascular mortality rate was lower than in the USA. In a recent study, 7175 Japanese subject free of cardiovascular disease at baseline were followed during 9.6 years. HDL-c was inversely correlated with total mortality (12).

Apolipoprotein A1 (Apo A1) levels predict CHD

Apo A1 is a surrogate marker for HDL-c and was measured in recent prospective epidemiological studies. A large study conducted in Sweden included 175,553 individuals (98,722 men with a mean follow-up of 66.8 months and 76,831 women with a mean follow-up of 64.4 months) (13). Apo A1 levels were inversely associated with myocardial infarction. The association remained in the multivariate analyses which included triglyceride levels. For example, in men below 70 years of age and in the lowest quartile of apo B, the risk ratio to suffer myocardial infarction was 1.4 in the lowest quartile of apo A1 when compared with the highest quartile (Figure 2). In the highest quartile of apo B, the risk ratio to suffer myocardial infarction was 4.0 in the lowest quartile of apo A1 when compared with the highest quartile. Similar relationship was found in older subjects and the relationship was stronger in women. The strength of the relationship between low HDL-c and increased risk of CHD was also greater in women than men in the meta analysis by Gordon et al. (10), the Framingham study (7) and the Atherosclerosis Risk in Communities (ARIC) study (14). Similarly, the InterHeart Study, a case–control study involving almost 30,000 participants in 52 countries, showed that an elevated Apo B/Apo A1 ratio accounted for more than half of the population-attributable risk for a first myocardial infarction (15) (Table 1). Interestingly, it was shown that apo A1 levels still predict the risk to present a cardiovascular event in patients being treated with statin. As shown in Table 2, in the

<table>
<thead>
<tr>
<th>OR adjusted</th>
<th>Attributable risk</th>
</tr>
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<tbody>
<tr>
<td>Smoking</td>
<td>2.27</td>
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<tr>
<td>Diabetes mellitus</td>
<td>3.08</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.48</td>
</tr>
<tr>
<td>ApoB/A1 ratio</td>
<td>3.87</td>
</tr>
<tr>
<td>Psychological factors</td>
<td>2.51</td>
</tr>
<tr>
<td>Phys. activity</td>
<td>0.72</td>
</tr>
<tr>
<td>Fruits &amp; vegetables</td>
<td>0.70</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.79</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>2.24</td>
</tr>
</tbody>
</table>

Figure 2 AMORIS study, results in men. 98,722 men and 76,831 women, follow-up 66.8 months. RR for MI (13)
AFCAPS-TexCAPS Trial, apo A1 levels were significantly associated with the risk of event (16). Taken together the strong and inverse association between apo A1 levels and CHD support the data obtained with HDL-c. However, in contrast to apo B, apo A1 is not a better marker than HDL-c. Measuring apo A1 might, however, be technically simpler as it can be easily standardised and can be done on frozen samples.

**Sequential changes of HDL-c predict future CHD event**

A cohort of 6928 subjects had at least two measurements of HDL-c separated by an average 2.6 years (17). Adjusting for covariates, a 10-mg/dl higher initial HDL-c was associated with a 11% (95% CI 7–14%) lower risk of coronary events. A 10-mg/dl increase in HDL-c between lipid measurements was associated with a 7% (95% CI 3–10%) lower risk of events. Neither initial nor change in triglycerides nor did LDL-c predict subsequent coronary events. The authors concluded that HDL-c measurements and changes in HDL-c predicted major adverse coronary events.

**Mixed hyperlipidaemia and cardiovascular disease**

Patients with mixed hyperlipidaemia (elevation of both plasma concentrations of LDL-c and triglycerides) display a high risk. Observations in cohort studies and in the placebo arm of interventions trials identified the mixed hyperlipidaemia as being associated with a threefold increase in the incidence of myocardial infarction when compared to patients with isolated hypercholesterolaemia (18). One of the key features of the mixed hyperlipidaemia is the association of both low HDL-c and high triglyceride to the elevated levels of LDL-c. Although other features of insulin resistance are prevalent in patients displaying this dyslipidaemia, the data are again consistent with a strong role of HDL-c in cardiovascular disease. These observations are highly relevant for clinicians who might underestimate the risk of patients with mixed hyperlipidaemia when compared with those displaying isolated hypercholesterolaemia, with higher total cholesterol levels. Similarly subjects with criteria for the metabolic disorder have a high risk of cardiovascular disease partly explained by low HDL-c (see below).

**Frequency of low HDL-c in patients with CHD**

In the screening phase of The Bezafibrate Infarction Prevention Trial, lipid and lipoprotein levels were obtained in approximately 6700 men and 1500 women aged 40–72 years. Mean HDL-c, progressively increased with age for both sexes (0.89 mmol/l at age of < 50 years to 0.96 mmol/l at age 65 or older in men and from 1.06 to 1.14 mmol/l for the respective age groups in women). The number of previous infarctions, severity of congestive heart failure and severity of angina were negatively correlated with mean HDL-c in a dose-response manner. Interestingly one patient of two (52%) with normal cholesterol level (total cholesterol below 5.13 mmol/l) exhibited HDL-c levels < 0.90 mmol/l (19).

In over 8500 community-living men with coronary artery disease mean HDL-c was 39 ± 11 mg/dl. In the whole population, 38% had low HDL-c (< 0.90 mmol/l), and 33% had high triglycerides (> 2.25 mmol/l). The authors also found that 40% of patients without a definite indication for cholesterol-lowering medications according to contemporary guidelines have low levels of HDL-c (6).

**Clinical evidence**

There are well-identified, genetically determined, hypohDLemias (defects in the apo A1 gene) associated with a dramatic increase of CHD (20). However, the issue is far more complex than for LDL-c as there are numerous exceptions with low levels of HDL-c and no cardiovascular disease. Dissecting the relationship between cardiovascular risk and very low levels of HDL-c shed light on the mechanism underlying the strong protective effect of HDL-c and the limit of a 'simple' measurement of HDL-c.

Lecithin: cholesterol acyl transferase (LCAT) is a key enzyme involved in intravascular maturation of HDL particles. Patients homozygote for mutation of the enzyme display dramatically low HDL-c, corneal opacities and renal disease. The clinical and biochemical status of large Canadian kindred with LCAT deficiency did not identify homozygosity for

| Table 2 Apo A1 predictive value AFCAPS/TexCAPS Logistic regression providing relation between lipid variables and major coronary events adjusted for age, sex, marital status, hypertension, smoking and family history of CHD (16) |
|-----------------|-----------------|-----------------|
| Value at baseline | Value at year 1 |
| LDL-c            | NS              | NS              |
| HDL-c            | NS              | NS              |
| Tg               | NS              | NS              |
| Apo A1           | 0.008           | 0.013           |
| Apo B            | 0.002           | < 0.001         |
LCAT deficiency as a risk factor for CHD. However heterozygosity was associated with increase intima media thickness and carotid atherosclerosis (21). This finding is similar to what was found for Tangier disease. This disease is caused by lack of a membrane cholesterol transfer protein (ABCA1) and affected subjects have orange tonsils but no other marked pathology (22). Heterozygosity for mutation in ABCA1 is associated with cardiovascular disease while homozygotes with Tangier disease do not display increased risk of cardiovascular disease. In these two metabolic disorders such paradoxical finding might be explained by other biochemical characteristics including low LDL-c and an efficient efflux of cholesterol from arterial wall. Apo A1 Milano is another example of a genetic disorder that paradoxically results both in low HDL-c and increased protection against heart disease (23). It also appears that this protective effect comes from the highly efficient efflux of cholesterol by mutant apo A1 (22). We identified a phenocopy of the disorder with similar propensity to protect against atherosclerosis despite a very low level of HDL-c (24).

HyperHDLemia was identified as a longevity factor more than 30 years ago by Glueck CJ et al. (25). These observations are highly consistent with the average HDL-c measured in healthy octogenarians in the Framingham Heart Study and studies in centenarians. Indeed, in Ashkenazi Jewish centenarians HDL-c levels were elevated and the lipoproteins were also found to be larger than controls (26). Finally (cholesterol ester transferase protein) CETP is another example of the complexity of the association between HDL metabolism and cardiovascular disease. Patients with abnormal CETP activity and high HDL-c levels are not consistently protected from CHD. Drugs inhibiting the enzyme activity are being developed and will help solve this issue. Moreover, these compounds act specifically on HDL-c with a limited effect on other lipoprotein (27). As explained below, the functionality of HDL particles might also be altered and subsequently this might limit the profound expected effect of the increase of HDL-c levels by CETP inhibitors. The clinical development programme of the CETP antagonist Torcetrapib has been recently discontinued after a significant increase in mortality was observed in a large placebo-controlled outcome study (ILLUMINATE) despite the drug’s impressive HDL raising effect. Although minor increases of blood pressure were observed with Torcetrapib, the mechanism responsible for the increased risk is unknown. Torcetrapib might have impaired HDL function, or alternatively a toxic effect not identified in phase 1–2 studies might have occurred.

Mechanistic evidence
Low-density lipoprotein carries cholesterol from the liver to peripheral tissues. When LDL-c levels are elevated a part is oxidised and subsequently taken up by the arterial wall to form atherosclerotic plaques. However, the cholesterol transport system based on HDL is responsible for facilitating the movement of cholesterol from tissues back to the liver. The so-called reverse cholesterol transport can be divided into three steps: (1) efflux of cholesterol from peripheral cells, (2) intravascular metabolism and remodelling of HDL and (3) uptake of cholesterol by the liver (Figure 3). In contrast to atherogenic apolipoprotein LDL and besides the reverse cholesterol transport, apo A1-containing HDL exert a spectrum of antiatherogenic activities among which are antioxidative, anti-inflammatory and anti-thrombotic actions (review in refs 28,29). These activities characterise functional HDL particles. Unfortunately, HDL functionality cannot be routinely evaluated. Small, dense HDL3 have elevated capacities to accept cellular cholesterol, to inhibit cellular expression of adhesion molecules and to protect LDL from oxidation when compared with large, light HDL2. Such potent antiatherogenic activities of small HDL can be, however, significantly altered in clinical conditions, such as metabolic syndrome as a result of profound alterations in HDL metabolism and composition; such alterations are primarily mediated by enhanced CETP activity on a metabolic background of hypertriglyceridaemia (27). Replacement of apo A1 by serum amyloid A under conditions of chronic inflammation usually encountered in metabolic syndrome may represent an additional mechanism contributing to the impairment of HDL antioxidative activity. Metabolic syndrome is, therefore, an example of a condition associated with dysfunctional HDL. This could explain why HDL3 is not identified as a better marker of cardiovascular disease when compared with larger particles.

Therapeutic evidence
It is beyond the scope of this review to analyse in depth that clinical trials which help assess the effect of increasing HDL-c on cardiovascular disease. In human, four different therapeutic approaches suggest that increasing HDL-c might indeed be beneficial: fibrate, nicotinic acid, statin and direct injection of HDL-like particles in patient with acute coronary syndrome. All fibrate derivatives share common hypolipidaemic effects characterised by a reduction in LDL-c, a marked reduction in plasma triglyceride levels and an elevation in HDL-c levels [see Table 3 taken from a
meta analysis of 50 trials (30)] and normalisation of the abnormal distribution of LDL particles (31–33). The Helsinki Heart Study, in which gemfibrozil was used as the hypolipidaemic agent, was the first trial demonstrating a beneficial effect of fibrate derivatives. Globally, a 34% reduction of cardiovascular events was observed (34). More recently, the VA-HIT trial confirmed the efficacy of gemfibrozil in a distinct population of patients selected on the basis of a low HDL-c (35). There was a 22% significant reduction of cardiovascular events. Interestingly, it was shown that the changes in HDL-c drive the benefit observed in these two trials (35–37). The BIP study and the FIELD studies were conducted in distinct population, i.e. subjects in secondary prevention (BIP) and diabetic patients in primary prevention (FIELD) (38–40). Despite the fact that both studies were negative with respect to the primary outcome, a significant reduction of events was found in the subgroups of patients with low HDL-c or in those with metabolic syndrome.

Of the available treatment options, nicotinic acid is the most potent agent for raising HDL-c. Average increase of HDL-c is almost twice the increase observed with fibrate while the effect on triglyceride and LDL-c is similar (41). The addition of nicotinic acid to primary statin therapy is a logical approach to dyslipidaemia management, given their complementary mechanism of action, and is supported by recent clinical trials such as the Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol-2 study.

Statins can also produce significant increases in HDL-C levels. The extent of this effect (+5 to +11%) depends on the molecule and the dose (42). The recent STELLAR (43) study assesses the lipid-modifying effects of rosuvastatin, atorvastatin, simvastatin and pravastatin. It demonstrated that rosuvastatin was the most potent statin to decrease LDL-c and increase HDL-c levels. The clinical significance of this statin-related increase in HDL-c is poorly known. In a recent post hoc (43) study pooling the results of

### Table 3

<table>
<thead>
<tr>
<th>Fibrates *</th>
<th>No. trials</th>
<th>No. subjects</th>
<th>Percent change HDL-c (%)</th>
<th>Percent change Tg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bezafibrate</td>
<td>12</td>
<td>5161</td>
<td>+11.0</td>
<td>−30.7</td>
</tr>
<tr>
<td>Ciprofibrate</td>
<td>2</td>
<td>91</td>
<td>+10.0</td>
<td>−45.0</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>15</td>
<td>1457</td>
<td>+10.2</td>
<td>−40.1</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>17</td>
<td>7461</td>
<td>+10.7</td>
<td>−47.9</td>
</tr>
<tr>
<td>Pooled</td>
<td>50</td>
<td>14,448</td>
<td>+10.0</td>
<td>−36.3</td>
</tr>
</tbody>
</table>

HDL-c and cardiovascular diseases

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several trials, the regression of coronary atherosclerosis (measured by angiography) in patients of the experimental vs. control group was attributable to the LDL-c lowering effect but also to the HDL-c increasing effects of the statin.

Recombinant apo A1 Milano/phospholipid complex produced significant regression of coronary atherosclerosis as measured by intracoronary ultrasound examination (Table 4) (44). Although of short duration and with a limited number of patients, this result adds to the evidence showing that HDL is a key factor in cardiovascular disease.

Rimonabant, a cannabinoid-1 receptor blocker decreased weight and increased HDL-c by 10%, an effect of same magnitude to what is observed with fibrates. Interestingly, half of the effect could not be explained by weight loss. The clinical relevance of this increase in HDL-c remains to be established with study assessing the progression of atherosclerosis and cardiovascular disease.

### Practical definition of low HDL-c

The inverse association between HDL-cholesterol concentrations and cardiovascular risk is a continuous; no threshold value has been identified. Thus, any categorical definition of low HDL-c is arbitrary. A cut-off of 0.90 mmol/l was initially proposed to define a low HDL-c. More recently, the NCEP-ATPIII increased this threshold to 1.03 mmol/l both in men and women. Women typically have higher HDL-c levels when compared with men, and a cut-point of 1.03 mmol/l identify more men than women with low HDL-c.Experts of the NCEP-ATPIII has rejected the idea of setting a higher cut-off to define low HDL-c for women because it would make many women who are otherwise at low risk eligible for LDL-lowering drugs. However, a higher level of HDL cholesterol (1.28 mmol/l) has been proposed as one of the five criteria defining the metabolic syndrome. In other words, in women with metabolic syndrome, a HDL-c lower 1.28 mmol/l, is already considered as low and need intensification of lifestyle modification to reduce the cardiovascular risk.

### Practical consequences for clinicians

All clinicians should be aware that HDL-c is one of the single strongest predictor of CHD and, therefore, needs to be measured in all patients at risk for CHD. A patient with HDL-c below 1.03 mmol/l triples his risk of coronary event when compared with a patient with HDL-c above 1.54 mmol/l.

In clinical practice the measurement of HDL-c may have a high level of variability for technical reasons. Thus one might consider repeating the measurement and/or measuring apo A1 albeit the measurement of apo A1 also lacks proper standardisation. To date, there is no simple measurements of a subpopulation of HDL which would significantly help the clinician to identify patients at risk. Indeed, the large particles seem to be a good marker in epidemiological studies whereas physiopathological findings suggest that the small particles do the proper cardio protective job.

The first step to consider in patients with low HDL-c is to look for specific causes and give advice to change inappropriate lifestyle components associated with low HDL-c, such as smoking, lack of physical exercise and overweight. In combinations, these recommendations can significantly increase HDL-c. Alcohol consumption is associated with higher levels of plasma HDL-C concentrations. However, high intake of alcohol increases the risk of CVD and cannot be recommended.

The varying consequences of HDL deficiency indicate that the lipid transport system it mediates is complex and that a low HDL must be understood in the context in which it occurs. Thus patients with very low HDL-c need a thorough evaluation by specialist physicians. Mild decrease of HDL-c has to be considered as one major CV risk factor. The global CV risk must be systematically evaluated by the physician.

In addition to the treatment of other risk factors and, when appropriate, statin therapy, fibrate and nicotinic acid are the best currently available approaches. It is also difficult to assess whether all fibrates are alike as we lack head to head comparisons. Taken together trials suggest that increasing

### Table 4 Effects of recombinant apoA1 Milano (ETC-216) administered during 5 weeks; Double-blind, randomised, placebo-controlled study in 57 patients. 47 subjects completed the study (42)

<table>
<thead>
<tr>
<th>No. patients</th>
<th>No. patients</th>
<th>Mean change from baseline</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>PCB 11</td>
<td>11</td>
<td>0.14</td>
<td>0.97</td>
</tr>
<tr>
<td>ETC-216 15 mg/kg</td>
<td>21</td>
<td>0.14</td>
<td>0.97</td>
</tr>
<tr>
<td>ETC-216 45 mg/kg</td>
<td>15</td>
<td>0.34</td>
<td>0.45</td>
</tr>
<tr>
<td>Combined 36</td>
<td>36</td>
<td>0.81</td>
<td>0.02</td>
</tr>
</tbody>
</table>
HDL-c is associated with a reduction of cardiovascular disease and the effect is predominantly observed in patients with low HDL-c.

References

15 Yusuf S, Hawken S, Ounpuu S et al. on behalf of the INTERHEART study investigators Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries. Lancet 2005; 366: 1640–49.
16 Goto AM, Whitney E, Stein EA et al. AFCAPS/TexCAPS Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis

37 Otvos JD, Collins D, Freedman DS et al. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. Circulation 2006; 113: 1556–63.


