PROCAM (Münster Heart Study)

HDL cholesterol and myocardial infarction

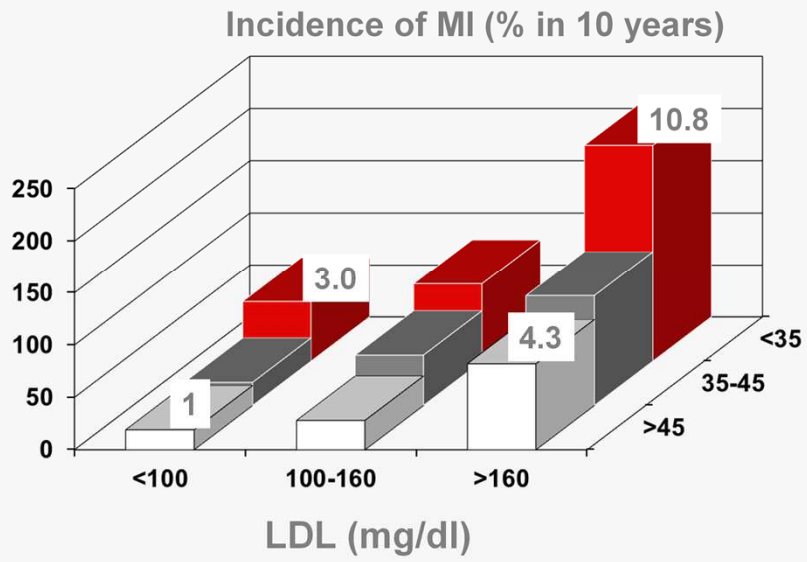
Clinical guidelines usually recommend that the level of high density lipoprotein cholesterol (HDL-C) should be measured. It is frequently argued that HDL-C levels below 35 mg/dl are causally associated with an increased risk of atherosclerosis. The information provided in this slide kit shows that this assumption is too simplistic and that the clinical interpretation of low HDL-C levels often requires expert knowledge.

Possible Relationship between Low HDL Cholesterol and Coronary Heart Disease

- **HDL is a surrogate marker for an atherogenic metabolic situation**
- **HDL is a disease marker for arteriosclerosis (negative acute phase reactant)**
- **HDL is a causal marker and anti-atherogenic**

The relationship between HDL cholesterol and coronary heart disease is complex and comprises at least three independent issues which are shown on this slide. Firstly, a low level of circulating high density lipoprotein cholesterol is a surrogate marker for an atherogenic metabolic situation commonly known as the metabolic syndrome, which also comprises the components obesity, hypertension, insulin resistance, and hypertriglyceridemia. Secondly, a low level of HDL cholesterol is a disease marker for advanced atherosclerosis which is related to its role as a negative acute phase reactant. Thirdly, several strands of evidence indicate that at a low level of circulating high density lipoprotein may be causally related to the development of atherosclerosis.

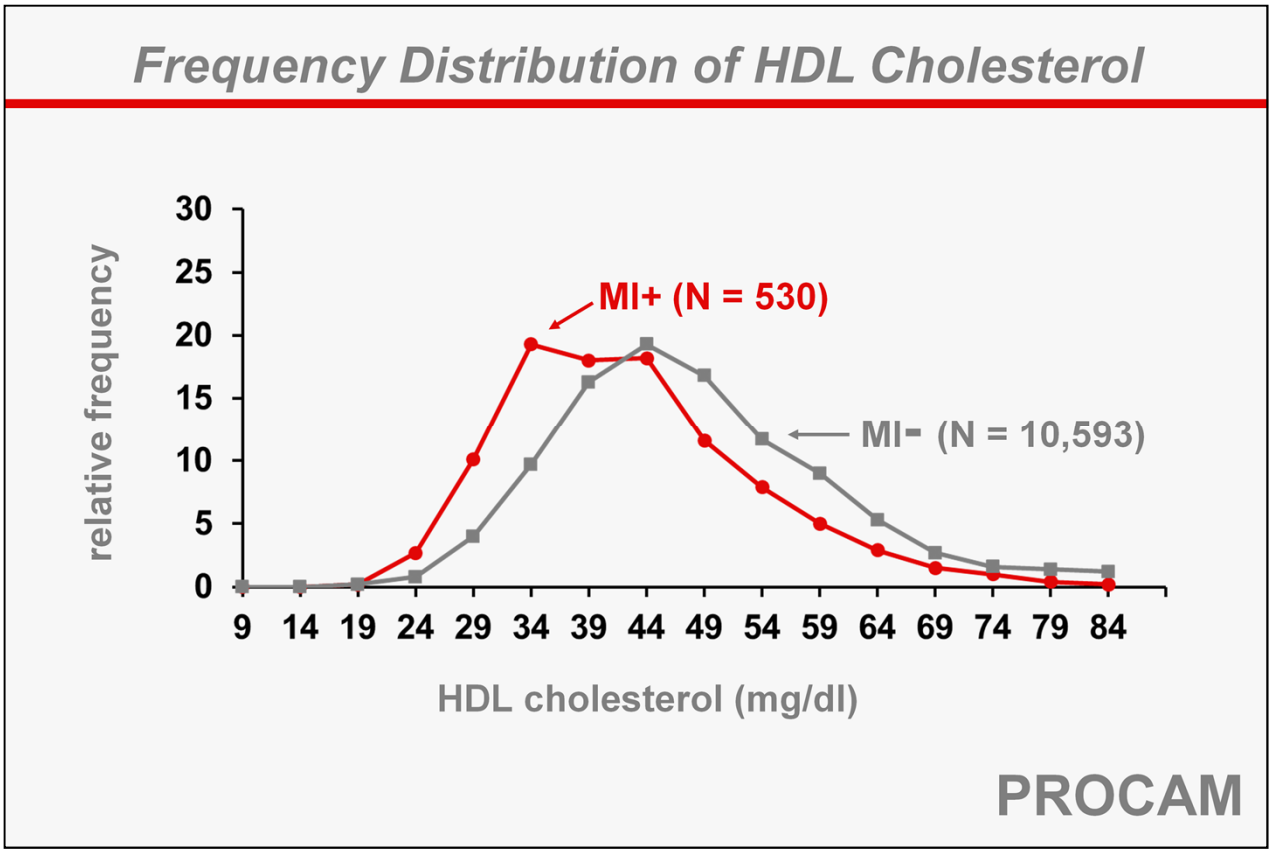
HDL Cholesterol: An Independent Risk Factor



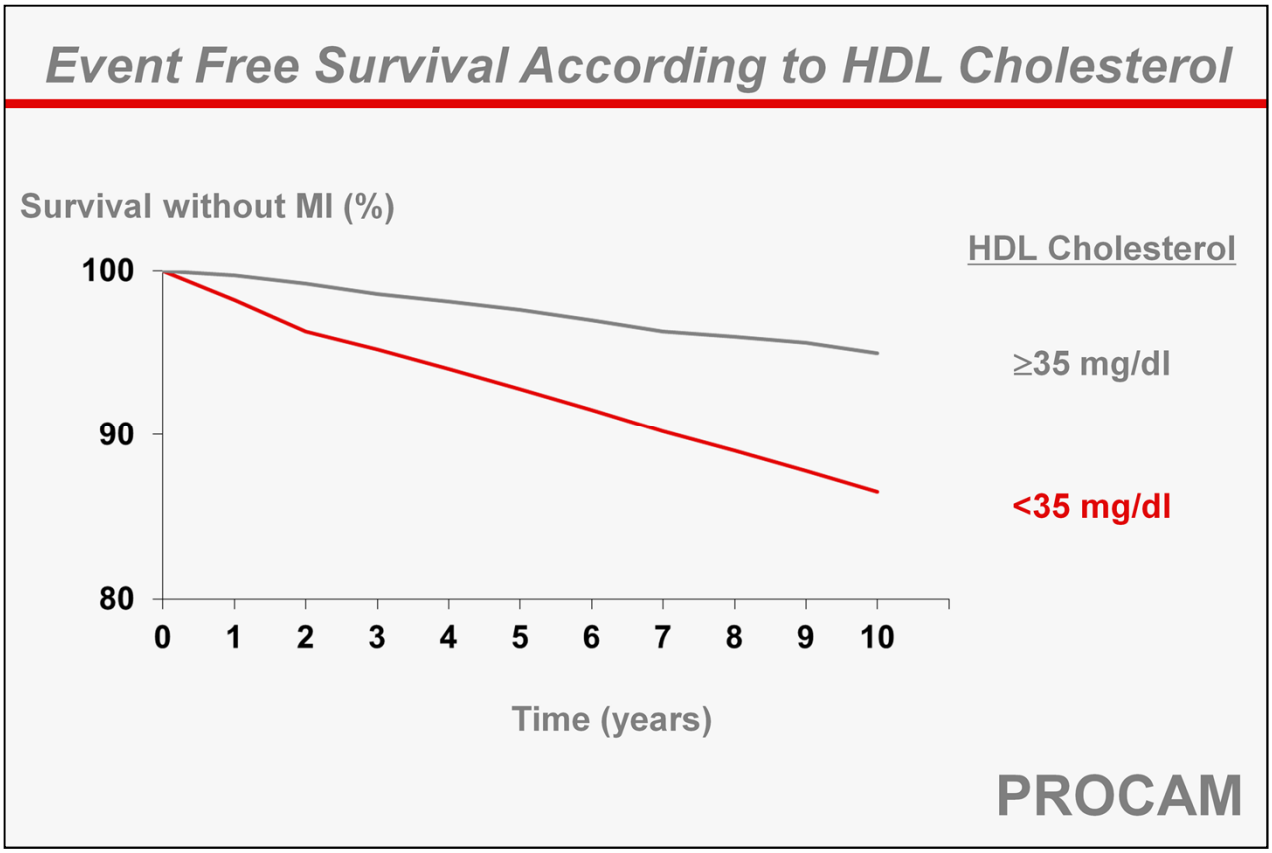
530 coronary events in 10 years in 11,123 men aged 35 to 65 years

PROCAM

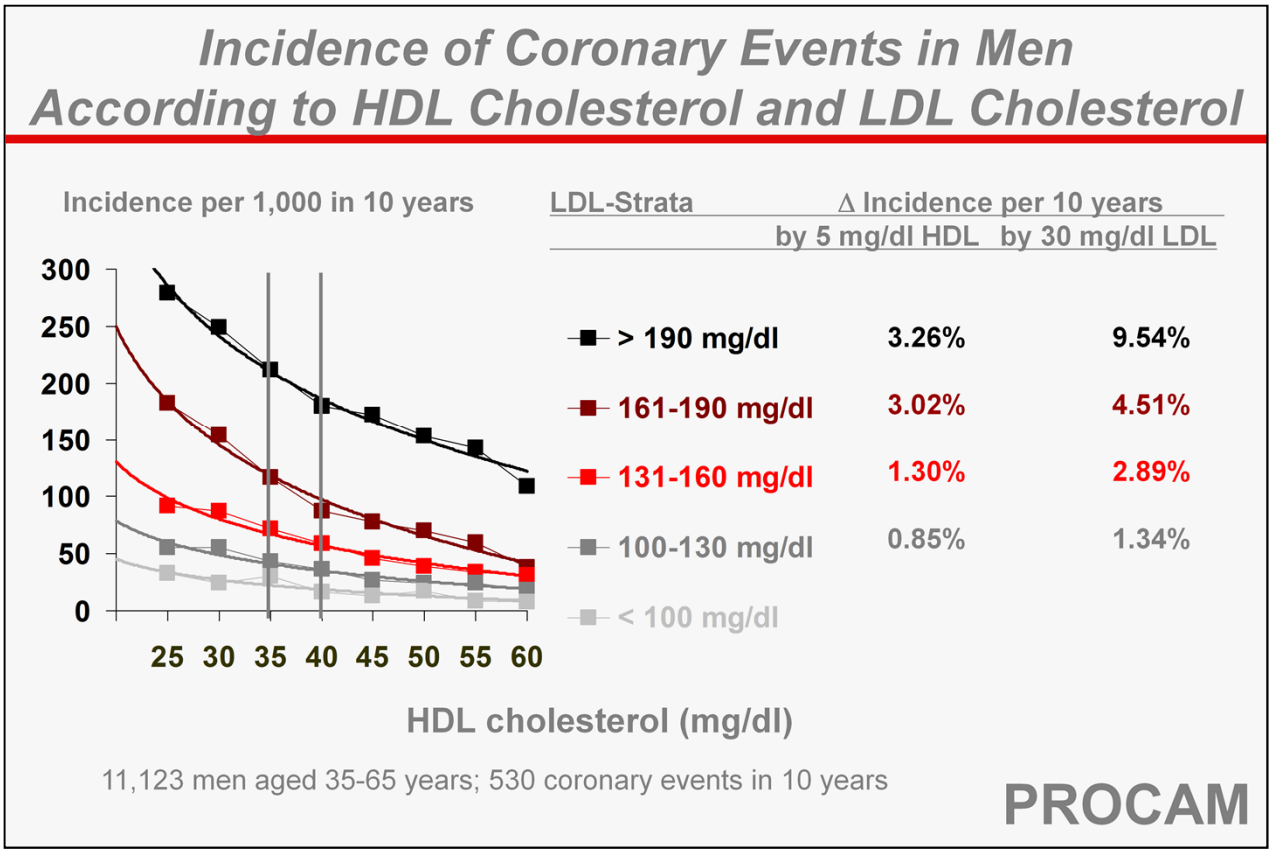
Perhaps the most important result to emerge from PROCAM and other prospective epidemiological studies of coronary heart disease risk factors is the finding that risk factors do not act in isolation, but in synergistic interaction with other risk factors. That is to say, individual risk factors interact in a multiplicative rather than an additive fashion. This is illustrated in this slide which shows the interaction between LDL cholesterol and HDL-cholesterol. Risk is 10.8-fold higher for men with LDL-cholesterol levels above 160 mg/dL and HDL-cholesterol levels below 35 mg/dL as compared to men with LDL cholesterol levels below 100 mg/dL and HDL-cholesterol levels above 45 mg/dL.



The frequency distribution of HDL-cholesterol differed pronouncedly between the 530 middle aged men who suffered a major coronary event in the PROCAM study as compared to the10,593 men who remained event-free within the 10-years follow-up period. Note that the HDL-cholesterol distribution is shifted considerably towards lower HDL-cholesterol levels in men who suffered a major coronary event. The peak frequency was located at HDL-cholesterol levels of 34 mg/dL in men who suffered a major coronary event as compared to 44 mg/dL in those who remained event-free. About 30% of men who experienced a major coronary event had HDL-cholesterol levels below 35 mg/dL



The event-free survival rate, expressed as percentage survival without MI, was significantly lower over the entire time range of the 10 years follow-up period among middle aged men with HDL-cholesterol levels below 35 mg/dL at study entry in the PROCAM study than for men with HDL-cholesterol levels equal or above 35 mg/dL.



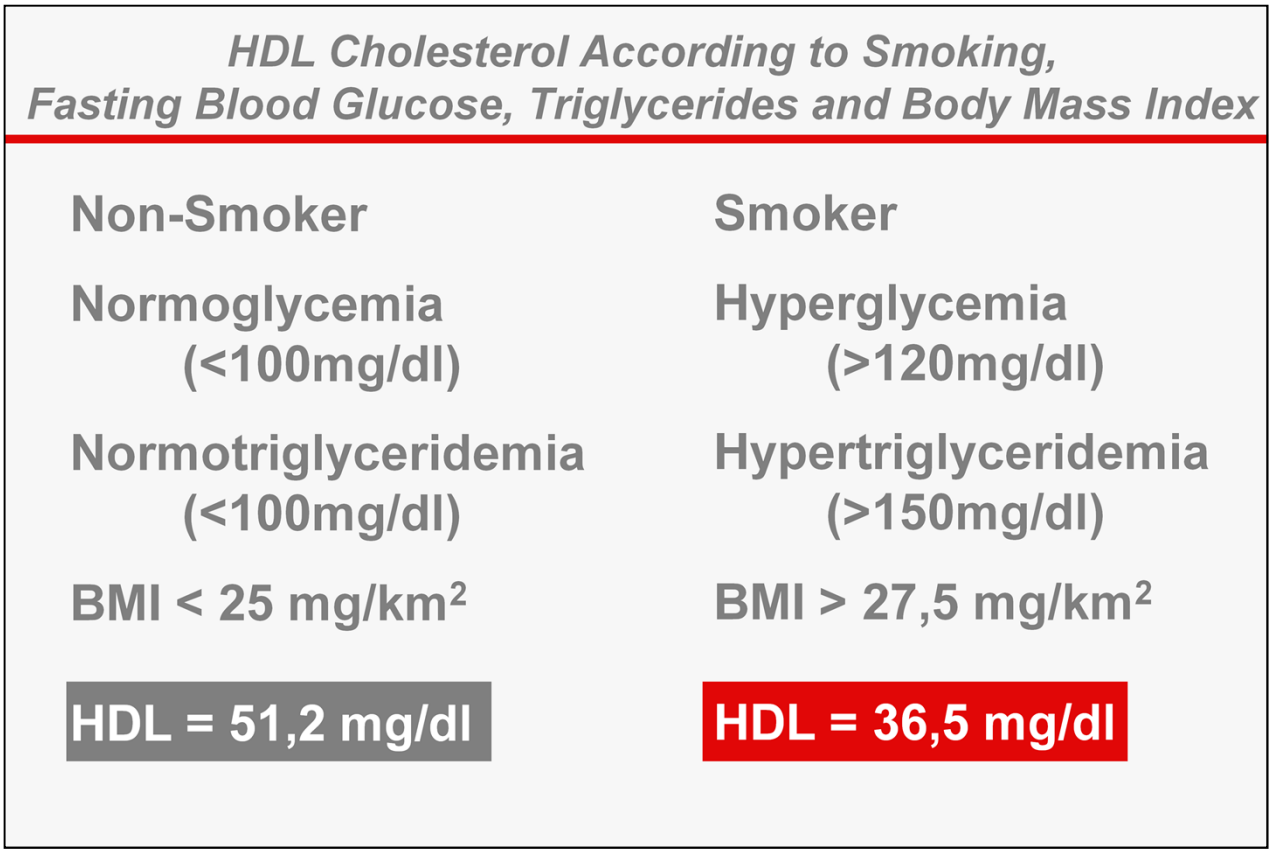
The slide shows the relationship between incidences per 1,000 at 10 years follow-up according to HDL-cholesterol and LDL-cholesterol levels. The expected effect of raising HDL-cholesterol by 5 mg/dL from 35 mg/dL to 40 mg/dL on the number of MI incidences depends on LDL-cholesterol levels. In men with LDL-cholesterol levels of >190 mg, the 5 mg/dL HDL-cholesterol increase would be expected to result in a 3.26% decrease of MI incidences. Similarly, a 3.02% decrease of MI incidences would be expected in men with LDL-cholesterol levels between 161 and 190 mg/dL, The corresponding numbers for men with LDL-cholesterol levels between 131 and 160 mg/dL or 100 and 130 mg/dL are 1.30% and 0.85%. No effect would be expected to result in men with LDL-cholesterol levels below 100 mg/dL. Also given are the percentage numbers expected to result from a decrease of LDL-cholesterol levels by 30 mg/dL.

Prevalence of Risk Factors in Male PROCAM-Participants

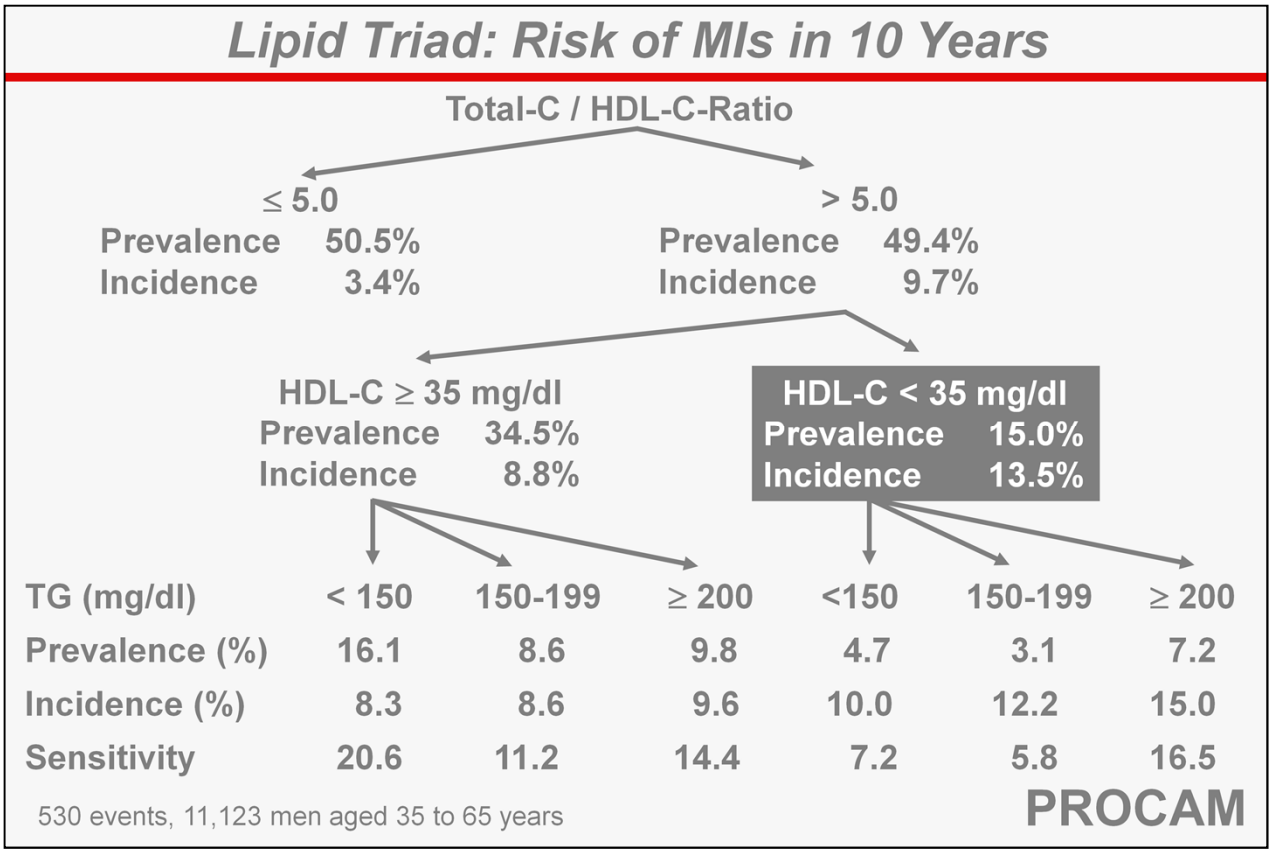
	< 35 mg/dl (n=1,715)	≥ 35 mg/dl (n=9,408)	p
Cigarette smoking	43.8	28.9	< 0.001
Diabetes mellitus	12.6	7.0	< 0.001
BMI > 30 kg/m^2	20.2	8.7	< 0.001
Triglycerides > 200 mg/dl	46.3	15.3	< 0.001
Hypertension	30.9	24.9	< 0.001
Family history of MI	19.3	17.3	n.s.
LDL cholesterol > 160 mg/dl	33.3	34.0	n.s.
MI incidence (in 10 years)	11.7	5.6	< 0.001

PROCAM

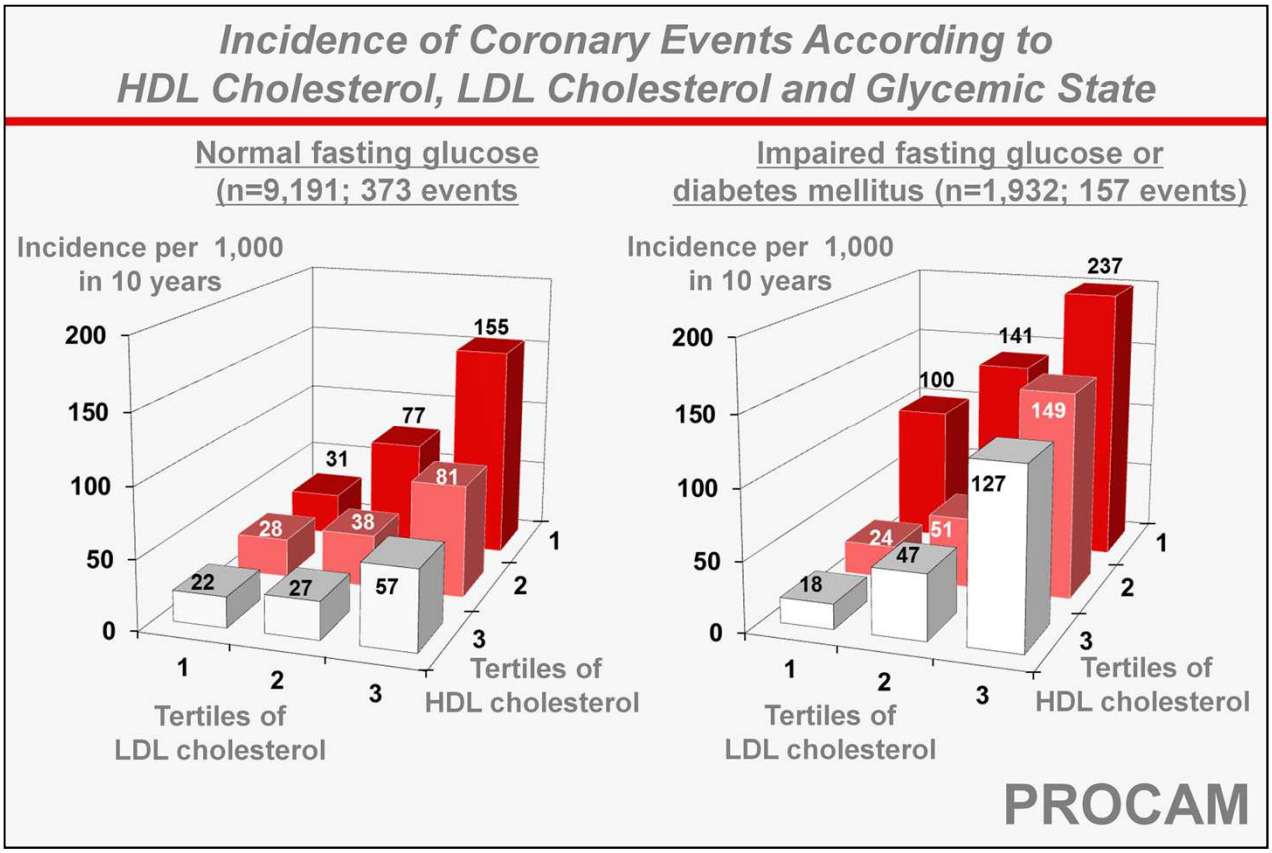
The prevalence of several well-established risk factors for coronary heart disease differs between male PROCAM participants with low and normal HDL-cholesterol levels. Thus, when the middle-aged men in the PROCAM study were divided into two groups, one with HDL cholesterol levels below to 35 mg/dl and the second with HDL cholesterol levels equal or above 35 mg/dl, cigarette smoking, diabetes mellitus, obesity, hypertriglyceridemia, and hypertension were all significantly more common in the men with low HDL cholesterol levels. On ten years follow-up, the incidence of MI in men with low levels of HDL cholesterol was more than twofold higher than in men with high HDL cholesterol levels.



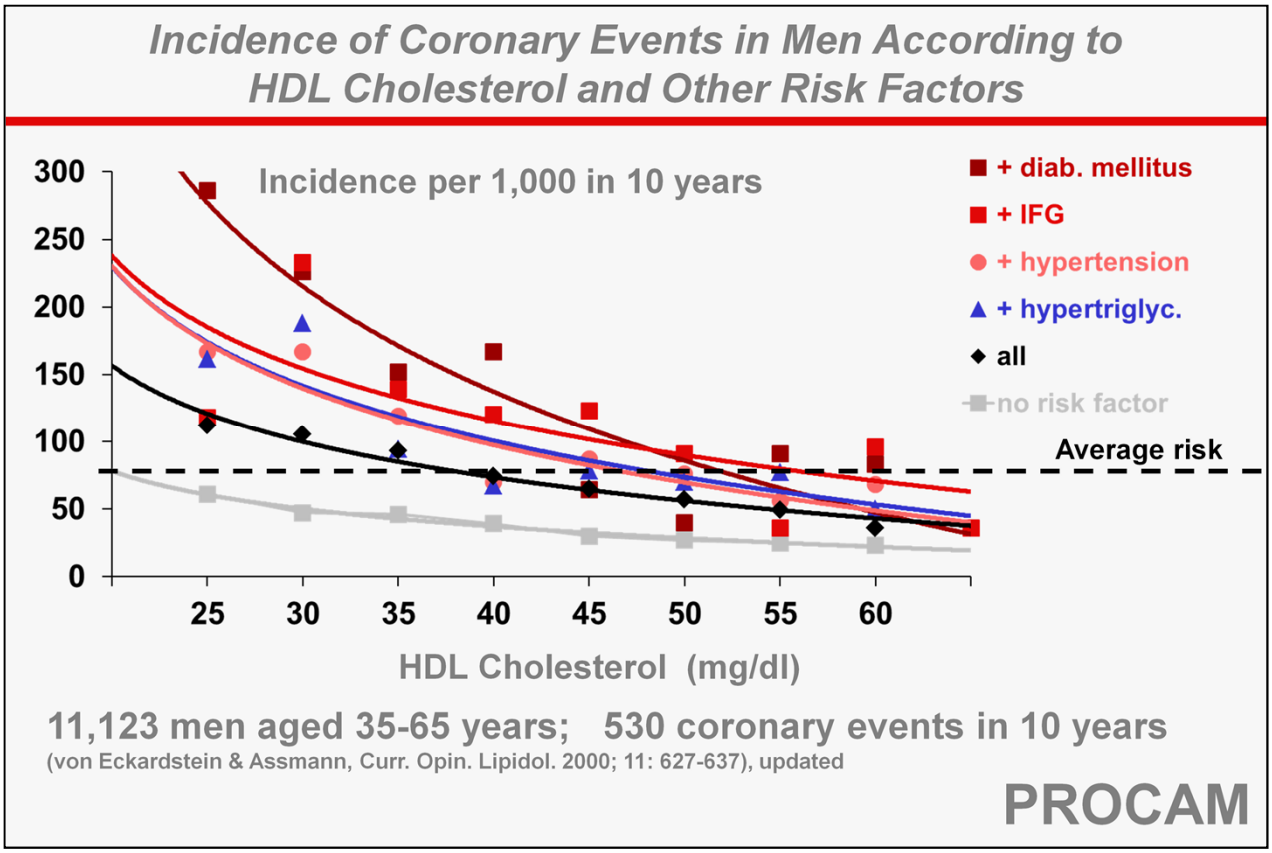
Typical male high risk patients are overweight smokers also having dyslipidemia and elevated blood glucose levels. If these patients are compared with lean low risk men, they are characterized by almost 15 mg/dL lower mean HDL-cholesterol levels.



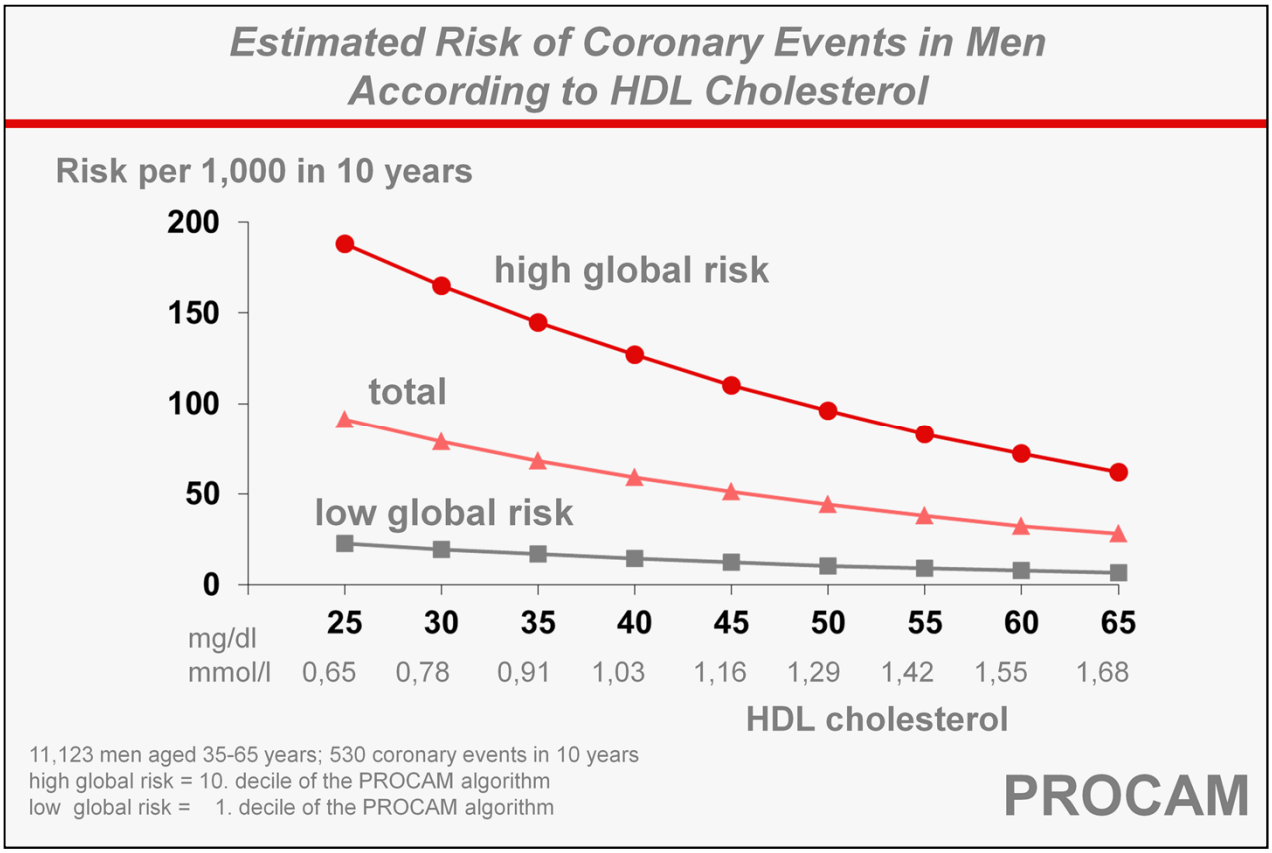
In recent years, much attention has been devoted to the so-called metabolic syndrome, a complex comprising insulin resistance, obesity, dyslipidemia and hypertension. One of the most commonly observed defects in this condition is the combination of moderately raised total cholesterol, low HDL-cholesterol, and hypertriglyceridemia (Lipid Triad). When the cohort of men aged 35 to 65 in PROCAM was segregated using a total to HDL-cholesterol ratio of 5 as a cut-off (the median in the population), and then further segregated according to the HDL-cholesterol and triglyceride levels, a striking gradient of risk was observed, ranging from 8.3% among men with an HDL-cholesterol equal or above 35 mg/dL (0.9 mmol/L) and a triglyceride level of below 150 mg/dL (1.7 mmol/L) to 16.5% among men with an HDL-cholesterol below 35 mg/dL (0.9 mmol/L) and a triglyceride level above 200 mg/dL (2.3 mmol/L).



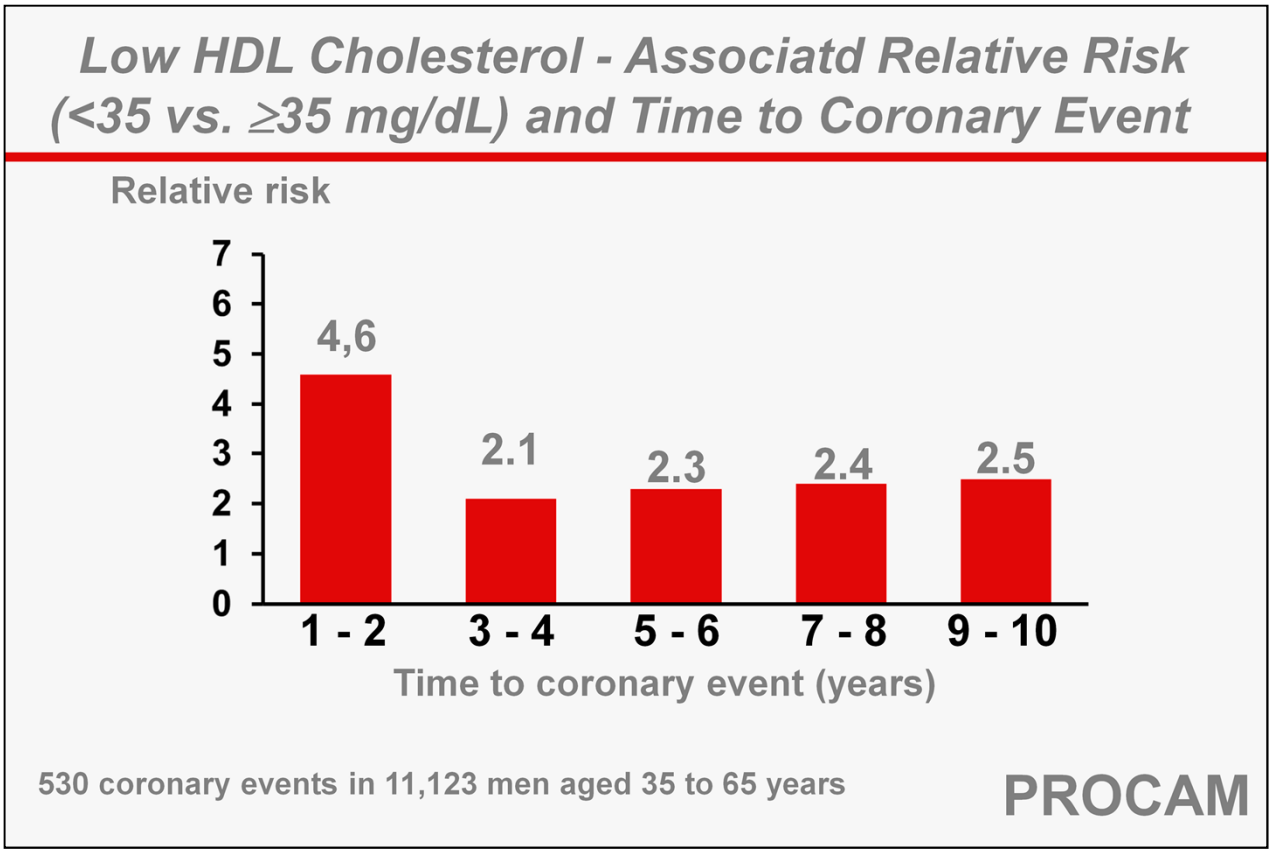
As has been noted above, one of the most commonly observed defects in the metabolic syndrome is the combination of raised LDL-cholesterol, low HDL-cholesterol, and elevated fasting blood glucose levels. This slide shows how impaired fasting blood glucose levels or the presence of diabetes mellitus in relation to HDL- and LDL-cholesterol levels influences the 10 years risk for a major coronary event in middle aged men in the PROCAM study. Note that there is a pronounced risk increase associated with an impaired glycemic state in almost all subgroups stratified according to LDL- and/or HDL-cholesterol levels.



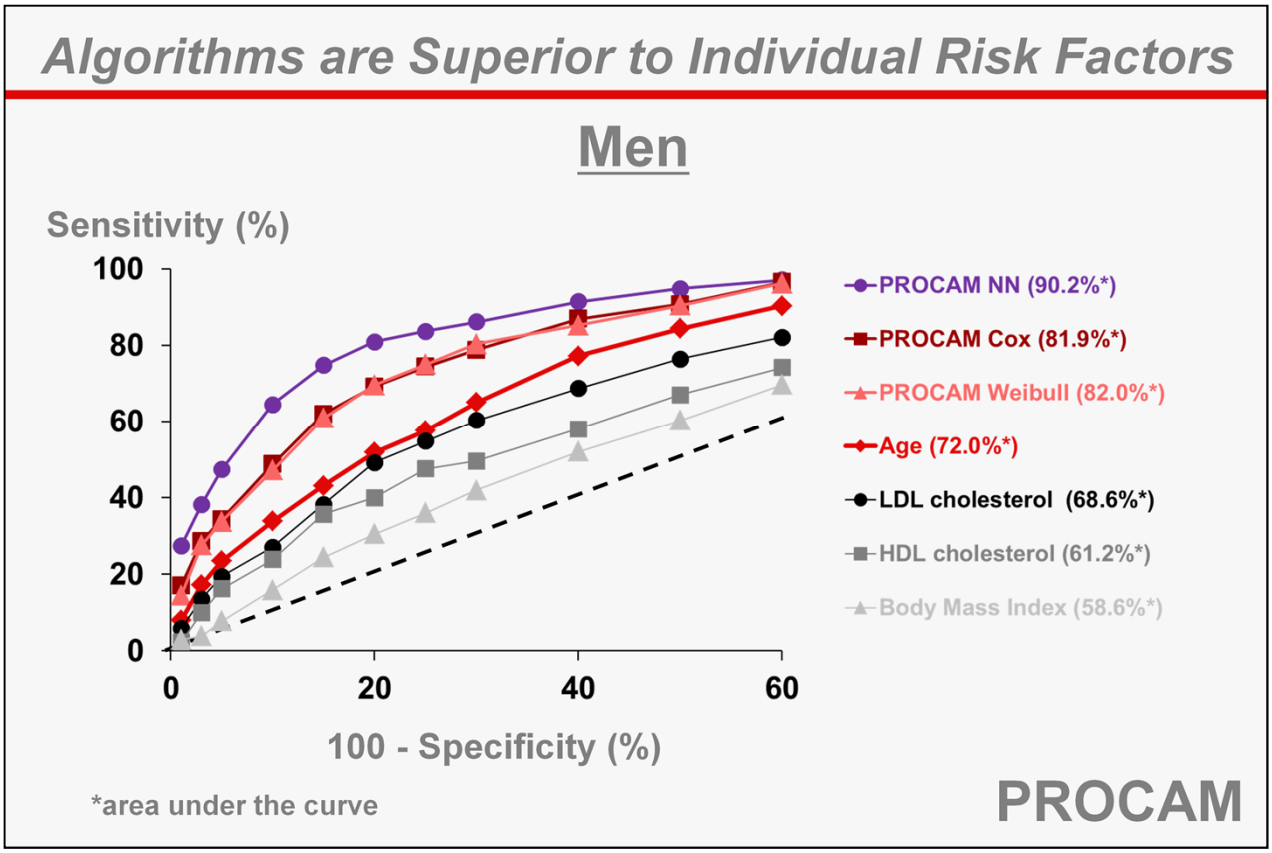
This slide shows the interaction of major coronary risk factors with HDL-cholesterol based on evaluation of 530 coronary events observed in 11,123 men aged 35 – 65 years within 10 years of follow-up. There is a steep increase of risk towards lower HDL-cholesterol levels in the presence of other risk factors, specifically with respect to increased fasting blood glucose (IFG) levels and the presence of diabetes mellitus. The dashed line masks the average risk of the studied population.



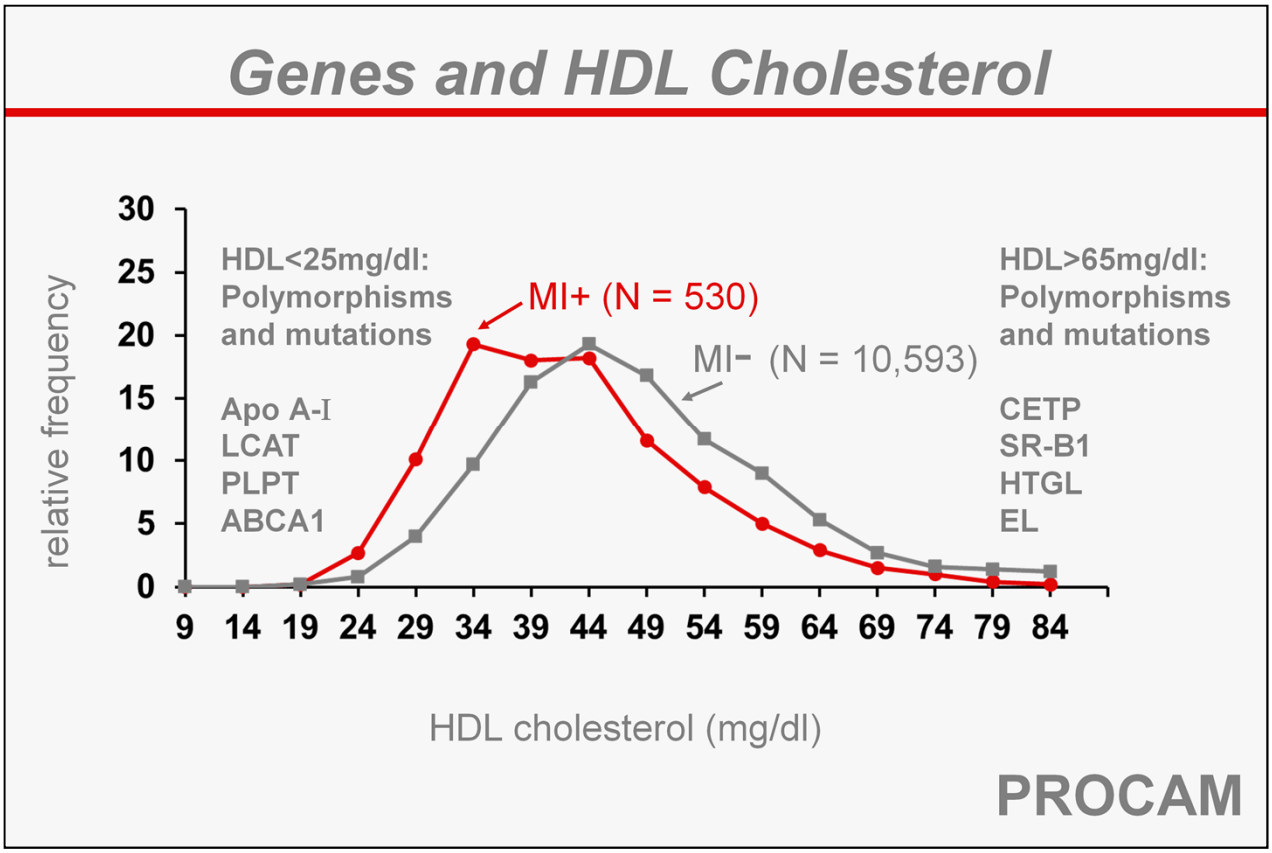
The estimated risk to suffer a major coronary event is shown according to HDL-cholesterol levels for middle-aged men with high global risk (representing the uppermost risk decile according to the PROCAM Cox proportional hazards model) and men with low global risk (representing the lowest risk decile according to the PROCAM Cox proportional hazards model). The relationship between between estimated risk and HDL-cholesterol levels for the entire population of men is shown for comparison. Note the steep increase in estimated risk towards lower HDL-cholesterol levels for men with high global risk.



This slide shows that the relative risk to suffer a coronary event within 1-2 years of follow-up was 4.6-times higher for men whose HDL-cholesterol levels were below 35 mg/dL than for men whose HDL cholesterol levels were equal or above 35 mg/dl. 3-4 years, 5-6 years, 7-8 years and 9-10 years after initial detection of a low HDL cholesterol level, the relative risk difference was still statistically significant, but the difference was evidently less pronounced. The reason for this observation may be that a low HDL cholesterol level is not only a marker of risk, but also a marker of advanced atherosclerosis based on the fact that HDL has the capacity to act as a negative acute phase reactant.



This slide shows receiver operating characteristic (ROC) curves obtained for HDL-cholesterol in comparison with corresponding curves obtained for body mass index (BMI), LDL-cholesterol, age, the PROCAM Cox model, the PROCAM Weibull model and neural network (NN) analysis. The ROC curve obtained for HDL-cholesterol alone was superior to BMI but distinctively inferior to the ROC curves obtained for LDL-cholesterol, age and all three algorithms.



It is known that HDL-cholesterol levels are influenced not only by dietary and life-style habits but also by genes. Although the precise role of genes in regulating HDL-cholesterol levels is currently unknown, a number of polymorphisms and mutations have been identified which affect HDL-cholesterol levels. HDL lowering variants have been found in the genes encoding apolipoprotein A-I (Apo A-I), lecithin:cholesterol-acyltranferase (LCAT), plasma phospholipid transfer protein (PLTP) and ABC-transporter ABCA1. HDL raising variants have been identified in the genes encoding cholesterol ester transfer protein (CETP), the scavenger receptor SR-BI, hepatic triglyceride lipase (HTGL) and endothelial lipase (EL).