
International Task Force for Prevention Of Coronary Heart Disease



Coronary heart disease and stroke: Risk factors and global risk

Slide Kit 6

PROCAM
(Prospective Cardiovascular 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.

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Slide 1:

PROCAM (Münster Heart Study):

Possible relationship between low HDL-cholesterol and coronary heart disease



***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**

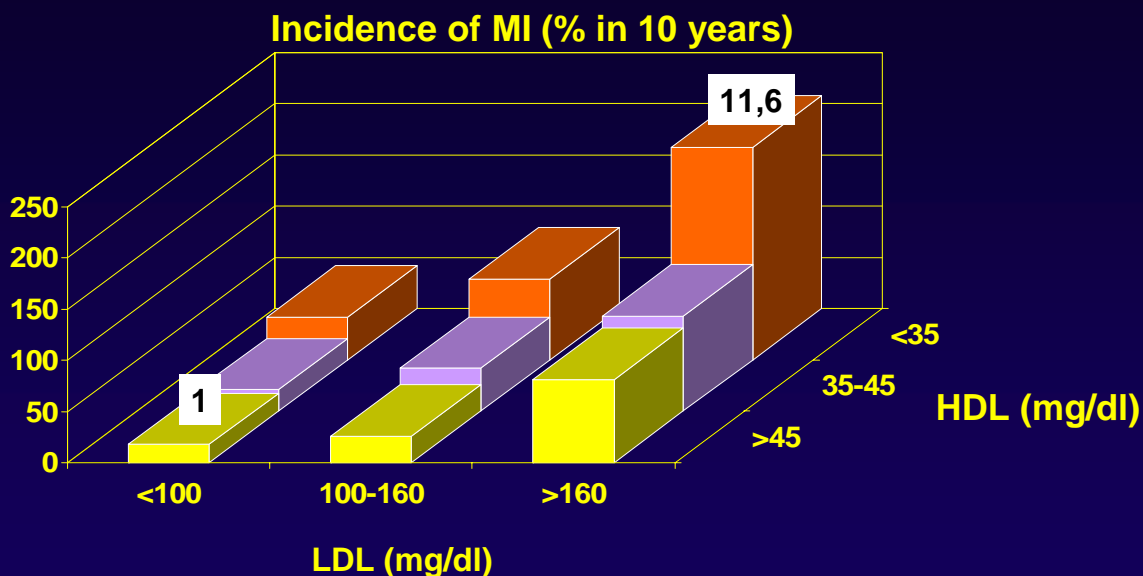
Possible relationship between low HDL-cholesterol and coronary heart disease

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.

Slide 2:

PROCAM (Münster Heart Study): HDL-cholesterol: an independent risk factor

HDL Cholesterol: An Independent Risk Factor



406 coronary events in 10 years in 7,152 men aged 35 to 65 years

PROCAM

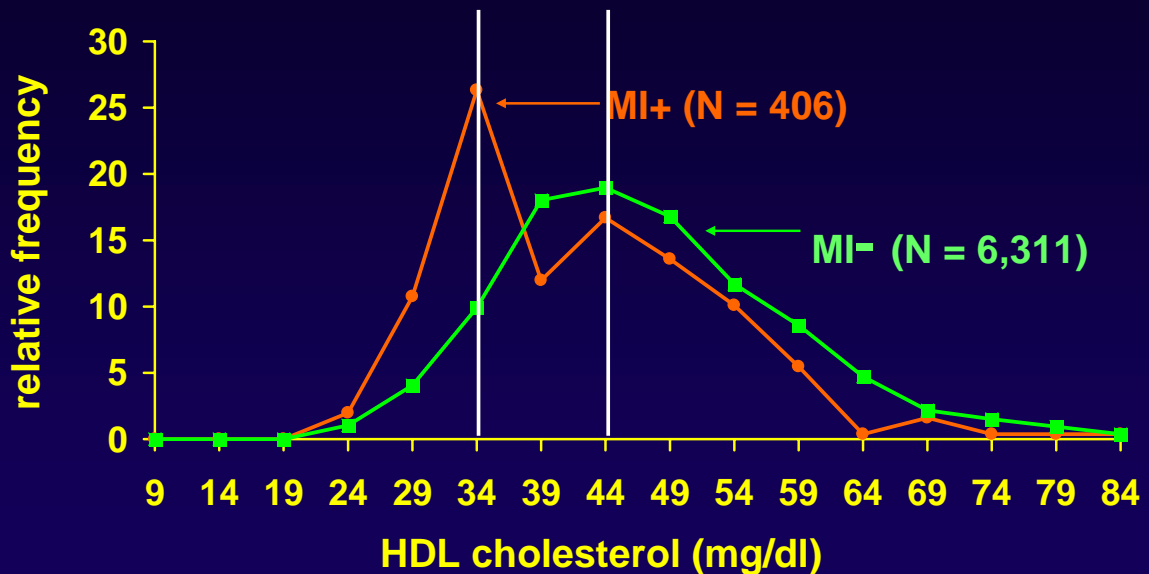
HDL-cholesterol: an independent risk factor

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 11.6-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.

Slide 3:

**PROCAM (Münster Heart Study):
Frequency distribution of HDL cholesterol**

Frequency Distribution of HDL Cholesterol



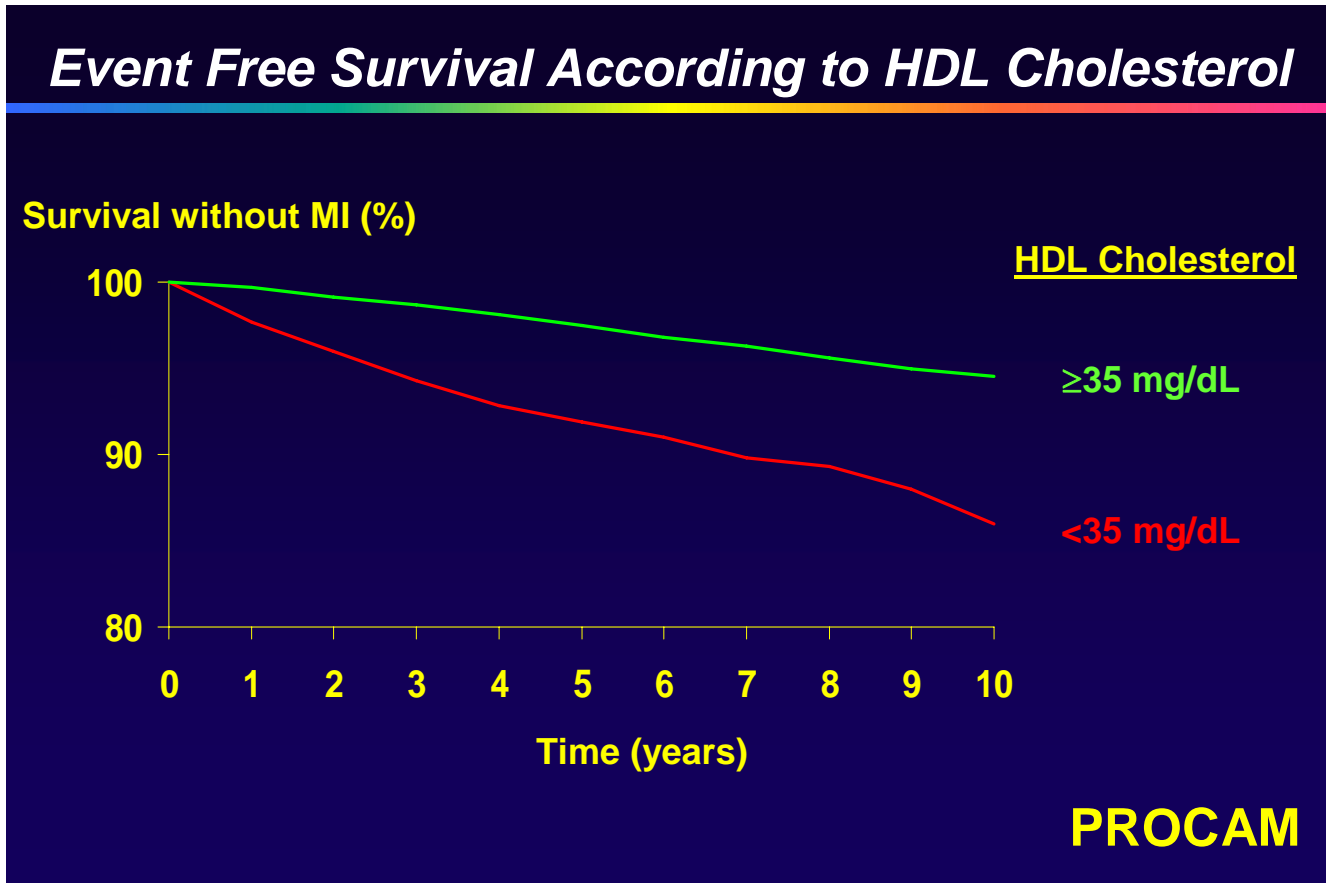
PROCAM

Frequency distribution of HDL cholesterol

The frequency distribution of HDL-cholesterol differed pronouncedly between the 406 middle aged men who suffered a major coronary event in the PROCAM study as compared to the 6,311 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 50% of men who experienced a major coronary event had HDL-cholesterol levels below 35 mg/dL.

Slide 4:

**PROCAM (Münster Heart Study):
Event-free survival according to HDL-cholesterol**



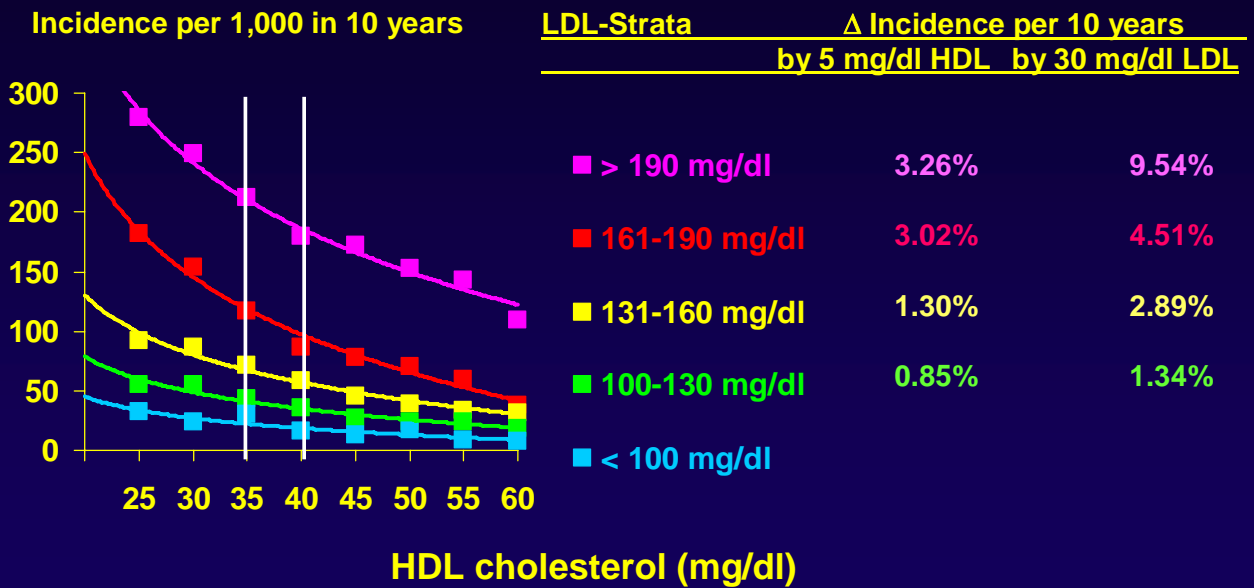
Event-free survival according to HDL-cholesterol

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.

Slide 5:

**PROCAM (Münster Heart Study):
 Incidence of coronary events in men according to HDL-cholesterol
 and LDL-cholesterol**

***Incidence of Coronary Events in Men
 According to HDL Cholesterol and LDL Cholesterol***



7,152 men aged 35-65 years; 406 coronary events in 10 years

PROCAM

**Incidence of coronary events in men according to
 HDL-cholesterol and LDL-cholesterol**

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.

Slide 6:

PROCAM (Münster Heart Study):

Prevalence of risk factors in male participants in the PROCAM study with low HDL cholesterol levels

Prevalence of Risk Factors in Male PROCAM-Participants

	< 35 mg/dl (n=1003)	≥ 35 mg/dl (n=5698)	p
Cigarette smoking	44.7	29.8	< 0.001
Diabetes mellitus	11.2	6.7	< 0.001
BMI > 30 kg/m²	18.7	8.5	< 0.001
Triglycerides > 200 mg/dl	42.2	15.3	< 0.001
Hypertension	29.5	26.5	< 0.05
Family history of MI	18.0	16.1	n.s.
LDL cholesterol > 160 mg/dl	32.5	34.0	n.s.
MI incidence (in 10 years)	11.9	5.1	< 0.001

PROCAM

Prevalence of risk factors in male participants in the PROCAM study with low HDL cholesterol levels

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.

Slide 7:

PROCAM (Münster Heart Study):

HDL-cholesterol according to smoking, fasting blood glucose, triglycerides and body mass index

***HDL Cholesterol According to Smoking,
Fasting Blood Glucose, Triglycerides and Body Mass Index***

Non-Smoker

**Normoglycemia
($<100\text{mg/dl}$)**

**Normotriglyceridemia
($<100\text{mg/dl}$)**

BMI $< 25 \text{ mg/km}^2$

HDL = 51,2 mg/dl

Smoker

**Hyperglycemia
($>120\text{mg/dl}$)**

**Hypertriglyceridemia
($>150\text{mg/dl}$)**

BMI $> 27,5 \text{ mg/km}^2$

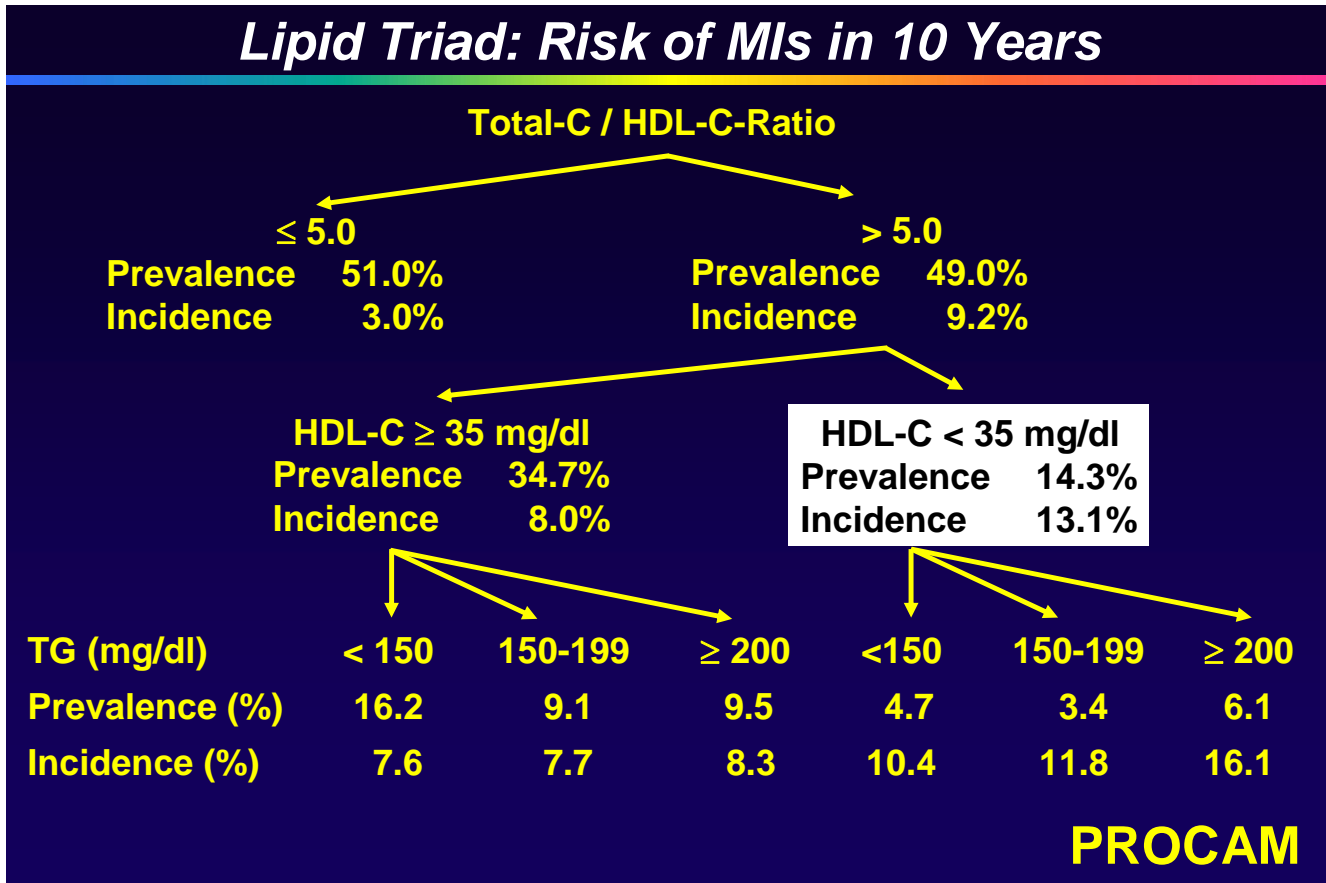
HDL = 36,5 mg/dl

HDL-cholesterol according to smoking, fasting blood glucose, triglycerides and body mass index

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.

Slide 8:

**PROCAM (Münster Heart Study):
 Lipd triad: risk of MI in 10 years**



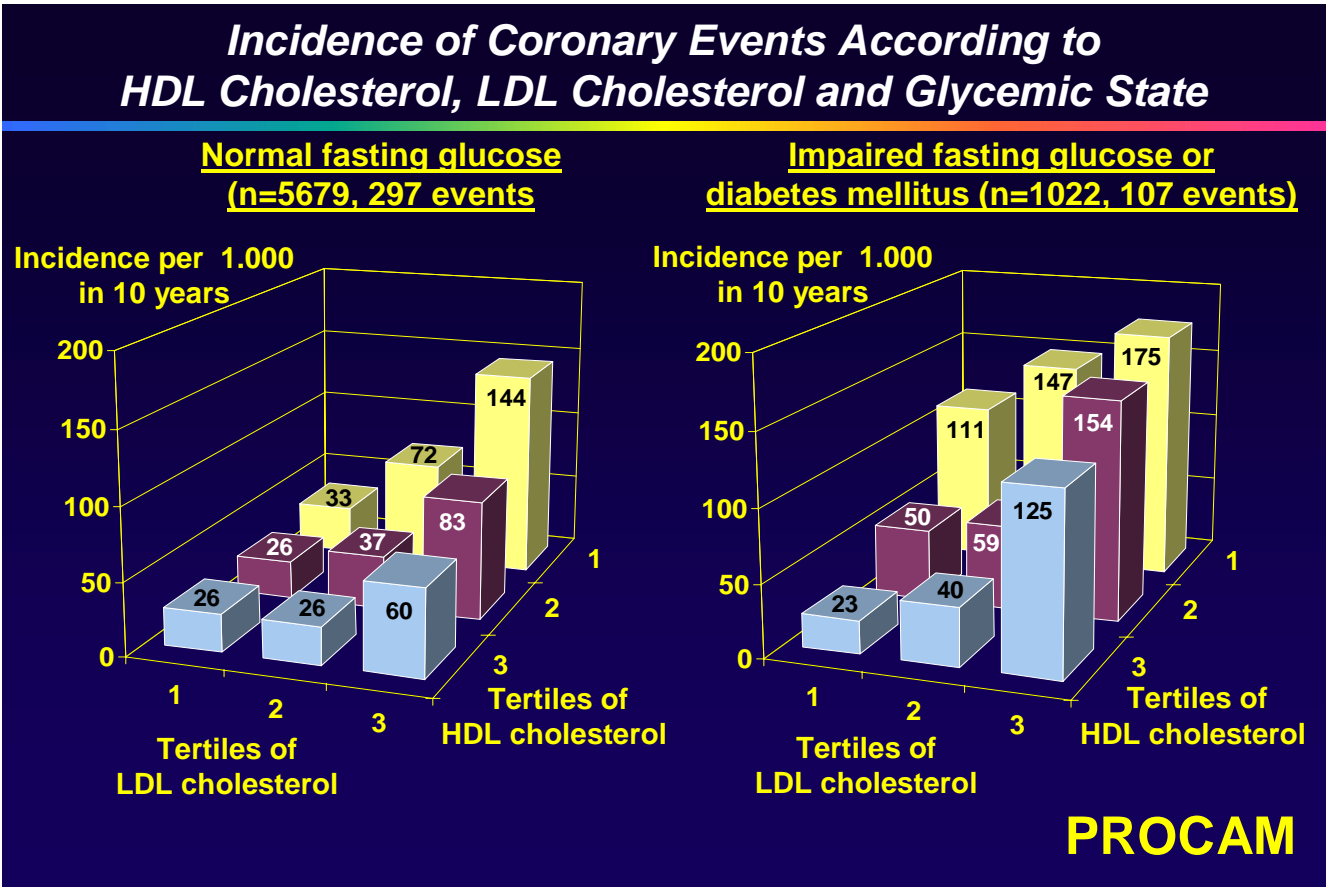
Lipd triad: risk of MI in 10 years

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 40 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 7.6% 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 16.1% among men with an HDL-cholesterol below 35 mg/dL (0.9 mmol/L) and a triglyceride level above 150 mg/dL (2.3 mmol/L).

Slide 9:

PROCAM (Münster Heart Study):

Incidence of coronary events according to HDL-cholesterol, LDL-cholesterol and glycemic state



Incidence of coronary events according to HDL-cholesterol, LDL-cholesterol and glycemic state

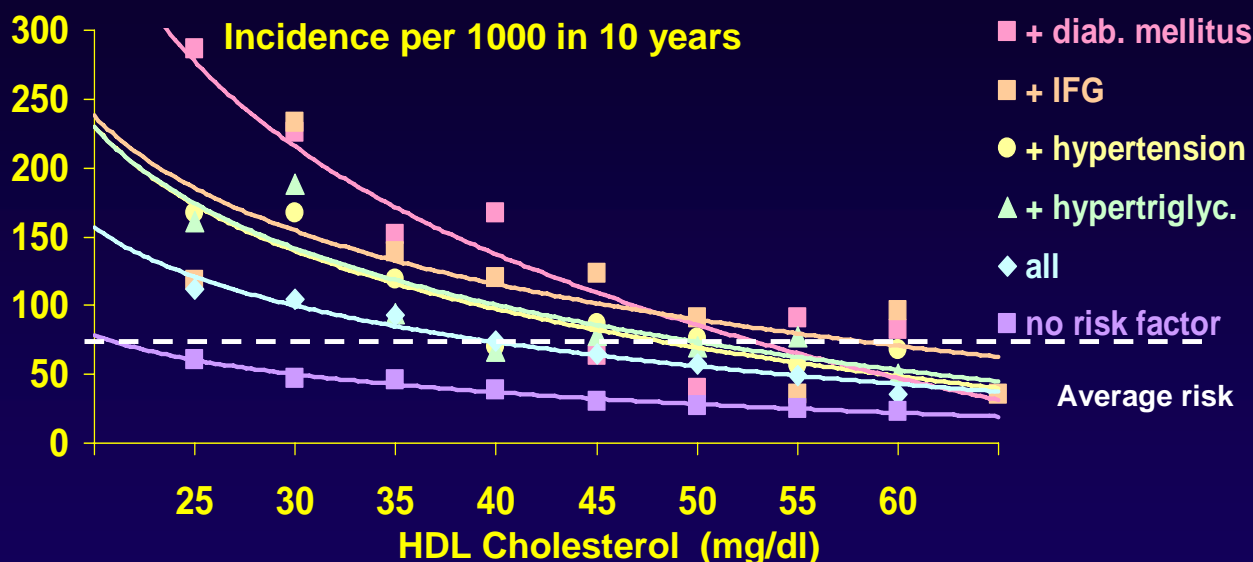
As has been noted above, one of the most commonly observed defects in the metabolic syndrome is the combination of raised LDL-cholesterol, low HDL-cholesterol, and elevated fasting blood glucose levels. This slide shows how impaired fasting blood glucose levels or the presence of diabetes mellitus in 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.

Slide 10:

PROCAM (Münster Heart Study):

Incidence of coronary events in men according to HDL-cholesterol and other risk factors

Incidence of Coronary Events in Men According to HDL Cholesterol and Other Risk Factors



PROCAM-Study: 4818 men aged 35-65 years; 325 coronary events in 10 years
(von Eckardstein & Assmann, Curr. Opin. Lipidol. 2000; 11: 627-637)

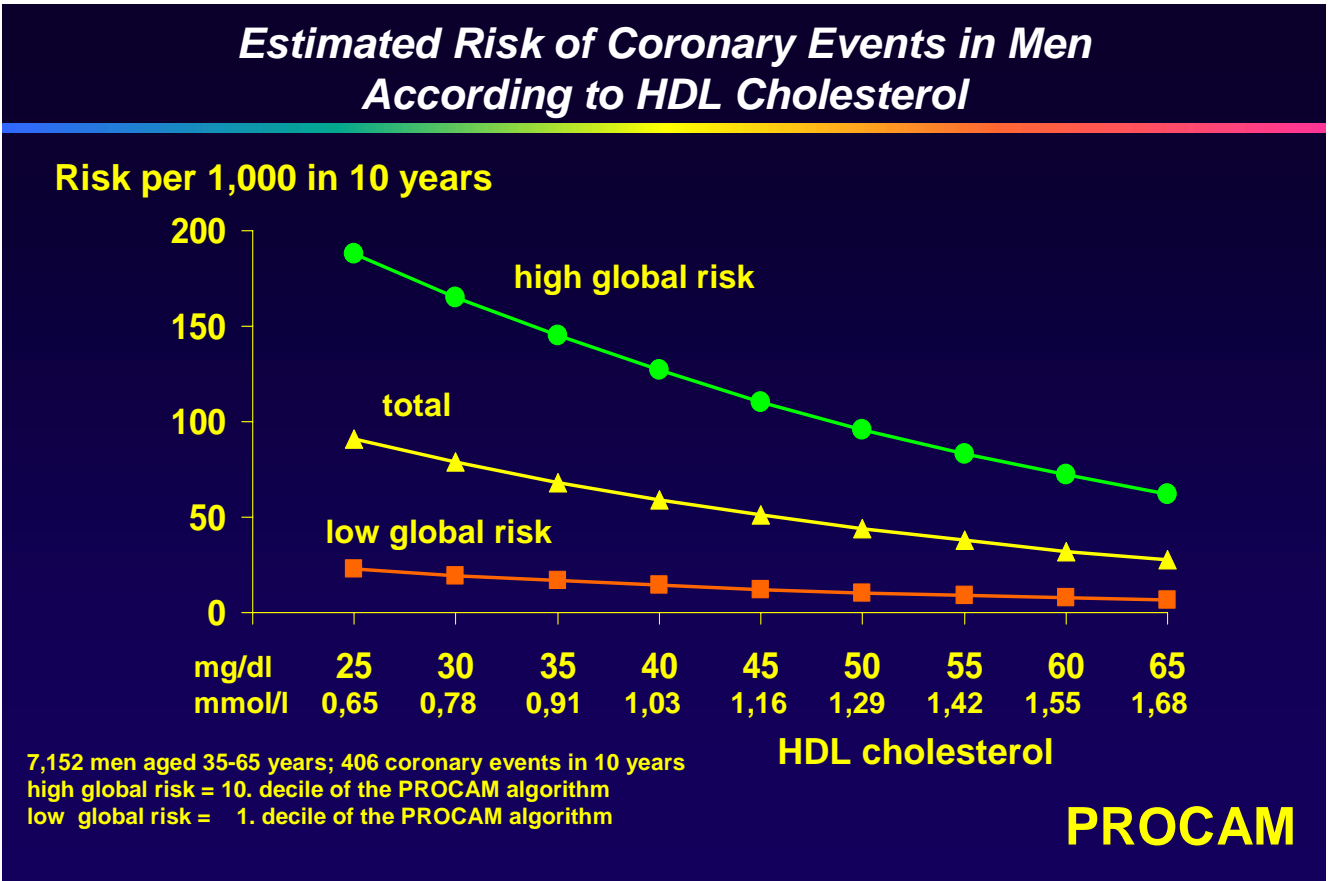
PROCAM

Incidence of coronary events in men according to HDL-cholesterol and other risk factors

This slide shows the interaction of major coronary risk factors with HDL-cholesterol based on evaluation of 325 coronary events observed in 4,818 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.

Slide 11:

**PROCAM (Münster Heart Study):
 Estimated risk of coronary events in men according to HDL-cholesterol**



Estimated risk of coronary events in men according to HDL-cholesterol

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 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.

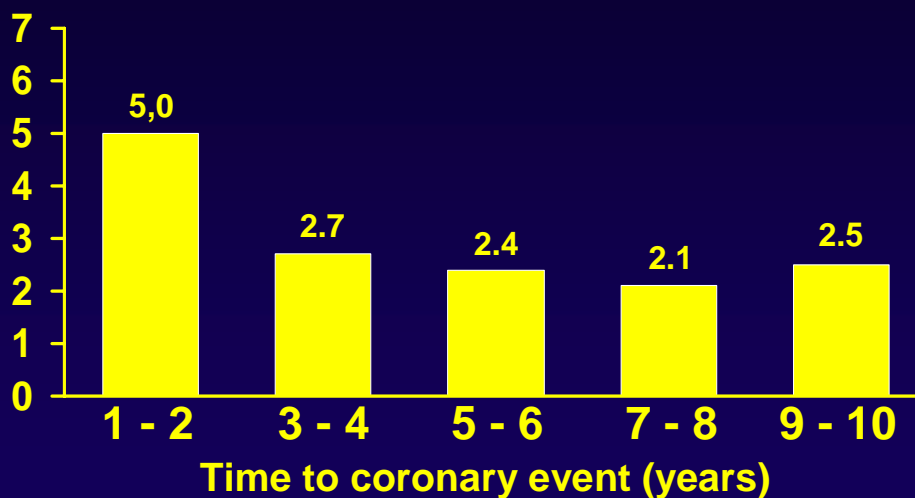
Slide 12:

PROCAM (Münster Heart Study):

Low HDL-cholesterol-associated relative risk (<35 versus \geq 35 mg/dL) and time to coronary event

Low HDL Cholesterol - Associated Relative Risk (<35 vs. \geq 35 mg/dL) and Time to Coronary Event

Relative risk



406 coronary events in 7,152 men aged 35 to 65 years

PROCAM

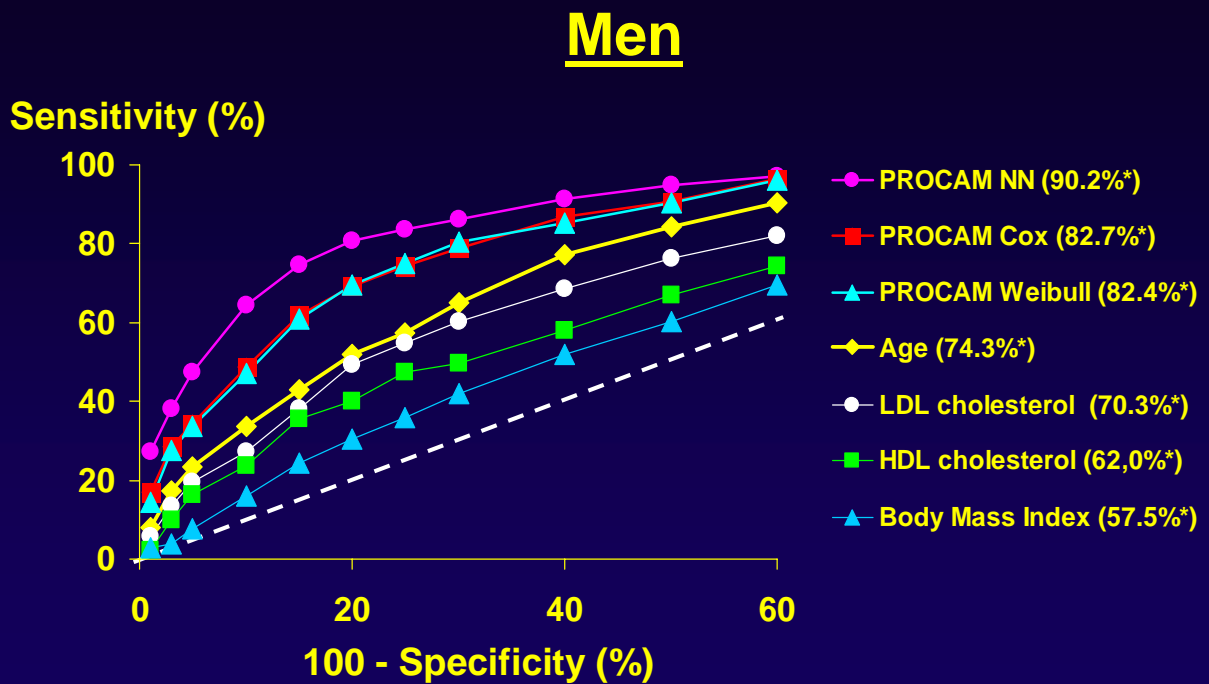
Low HDL-cholesterol-associated relative risk (<35 versus \geq 35 mg/dL) and time to coronary event

This slide shows that the relative risk to suffer a coronary event within 1-2 years of follow-up was 5-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.

Slide 13:

**PROCAM (Münster Heart Study):
Algorithms are superior to individual risk factors**

Algorithms are Superior to Individual Risk Factors



PROCAM

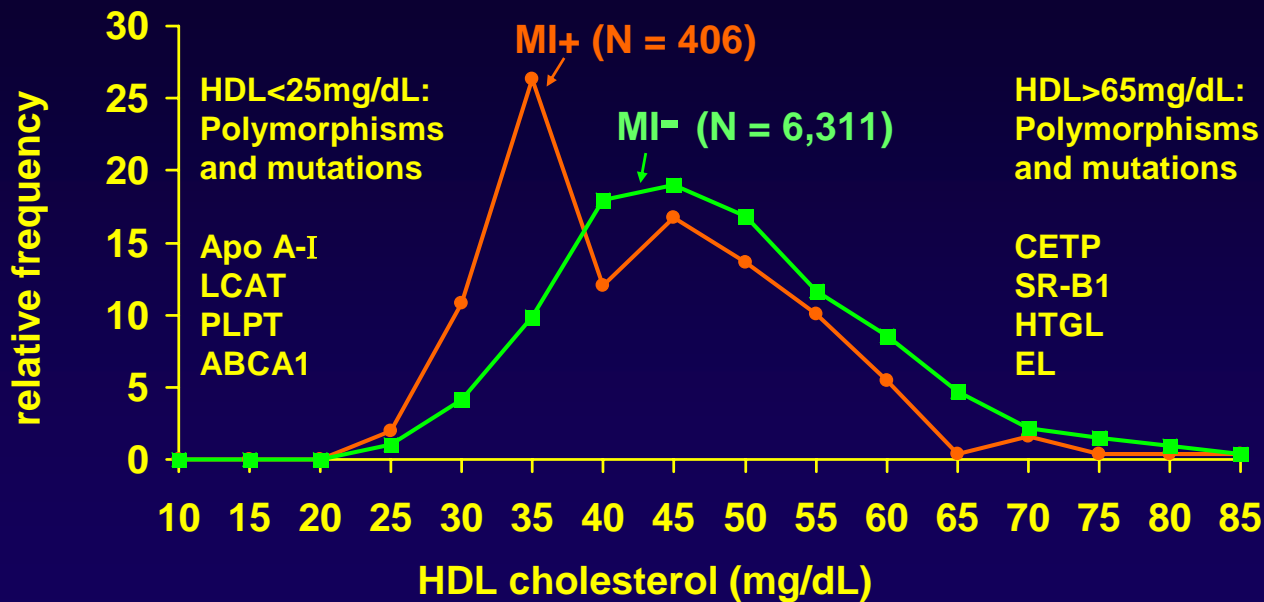
Algorithms are superior to individual risk factors

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.

Slide 14:

**PROCAM (Münster Heart Study):
 Genes and HDL-cholesterol**

Genes and HDL Cholesterol



PROCAM

Genes and HDL-cholesterol

It is known that HDL-cholesterol levels are influenced not only by dietary and lifestyle 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-acyltransferase (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).