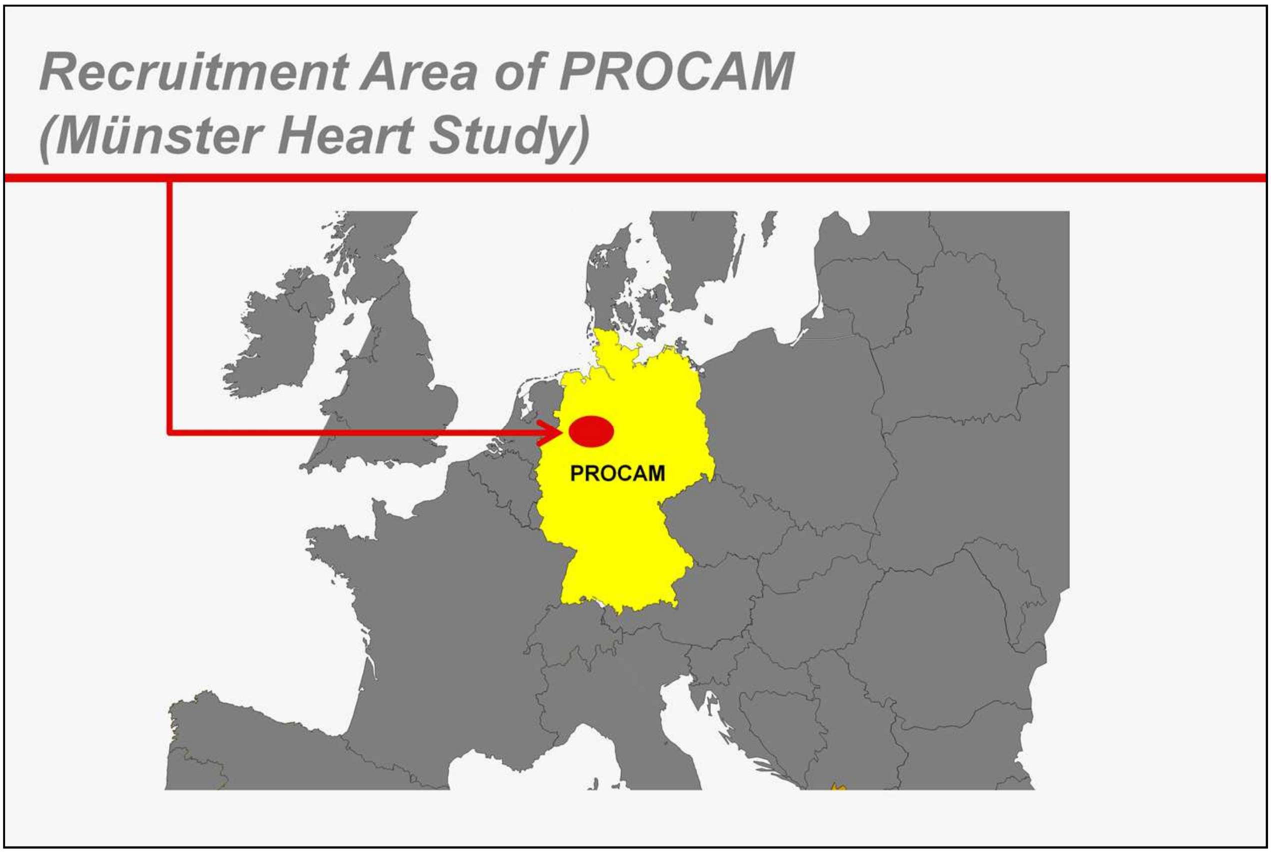
PROCAM (Münster Heart Study)

Design and principal results of the Prospective Cardiovascular Münster (PROCAM) study

The **Pro**spective **Ca**rdiovascular **M**ünster (PROCAM) Study (also known as the Münster Heart Study) was initiated in 1978 by the Institute of Arteriosclerosis Research at the University of Münster. In several waves of recruitment, precisely 50.000 participants aged between 16 and 65 years were recruited from among the employees of 84 large companies and the public service in Münster and the northern Ruhr area, the area shaded on the slide. All participants are in continuing long term follow-up for heart disease, stroke and mortality.



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Design of the Study

* beginning of the study 1978
* precisely 50.000 volunteers (one third women, two thirds men)
* age range 16 to 65 years
* employees of 84 large companies and the public service in Münster and the Northern Ruhr Area
* rate of participation on average 60%

* examination and interview by physician (standardized questionnaires)
* measurement of blood pressure and anthropometric data
* resting electrocardiogram
* case history and family history
* collection of blood sample after 12-hour fast (>30 laboratory parameters)

* examination carried out during paid working hours
* all findings were reported to the participant´s general practitioner
* the investigators neither carried out nor arranged for any intervention

* questionnaires were sent to the participants every 4 years for follow-up
* examination repeated after 6 to 7 years

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This slide shows the main characteristics of the PROCAM Study.

Participants

	Men	Women	Total
until July 2007	31,376 (62,8%)	18,624 (37,2%)	50,000
current longitudinal analysis (July 2007)	26,245	14,163	40,408
No. of participants with full data	22,798	8,954	31,752

PROCAM

This slide shows the main characteristics of the PROCAM Study.

Outcome in Individuals with Follow-up of 27 Years, mean 12 Years

	Men	Women
Age range	20-65	20-65
Participants	22,798	8,954
Nonfatal MI and CHD deaths	627	62
Cerebrovascular events	184	35
Cancer deaths	518	138
other Deaths (except CHD, CVD and cancer)	515	121

PROCAM

This slide shows the main characteristics of the PROCAM Study.

Outcome (Men)

- 11,675 men aged between 35 and 65 years
  - no prior history of myocardial infarction or stroke
  - fixed follow-up period of 10 years
  - recrutement period 1978-1995
- 530 definite coronary events:
  - 76 sudden cardiac deaths
  - 88 fatal myocardial infarctions (MI)
  - 366 definite non-fatal MI
- 84 cerebrovascular events:
  - 70 non-fatal cerebrovascular events
  - 14 fatal strokes
- 432 deaths of non-coronary and non-cerebrovascular origin:
  - 253 cancer
  - 14 suspected coronary deaths
  - 26 other diseases of the circulatory system
  - 61 other diseases
  - 60 accidental or violent deaths
  - 18 unknown cause of death
- 97 with CHD (coronary angiography patients)
- 36 with revasculation procedurs
- 10,593 men survived 10 years without definite nonfatal MI or stroke

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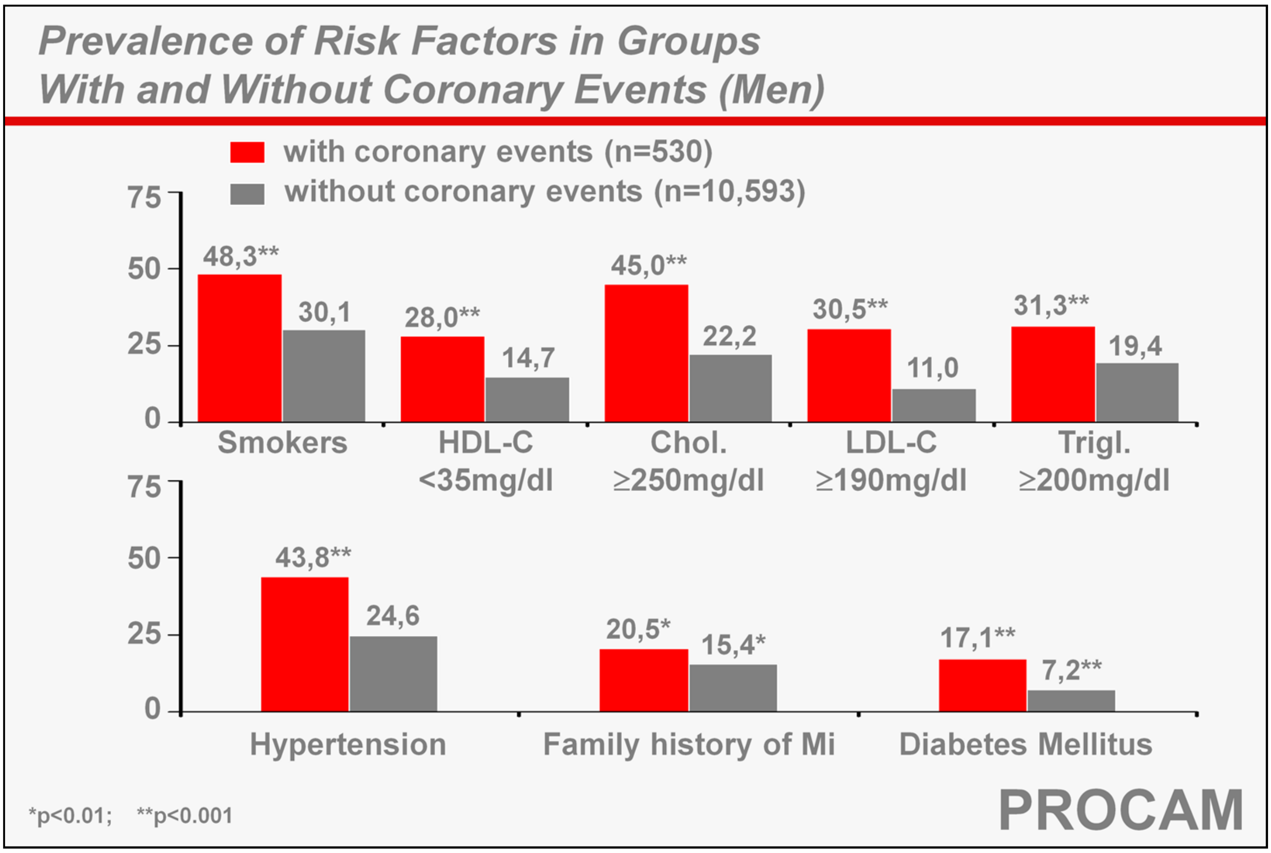
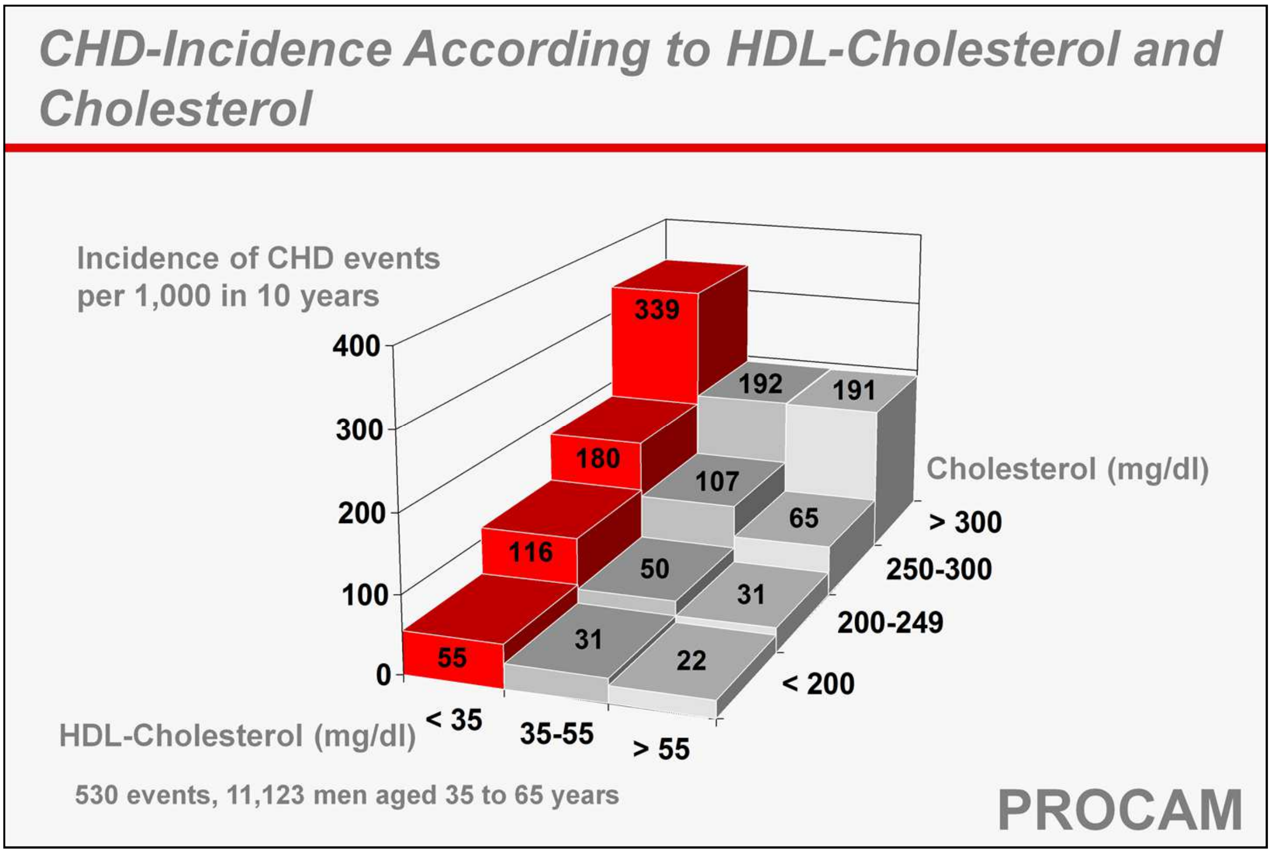
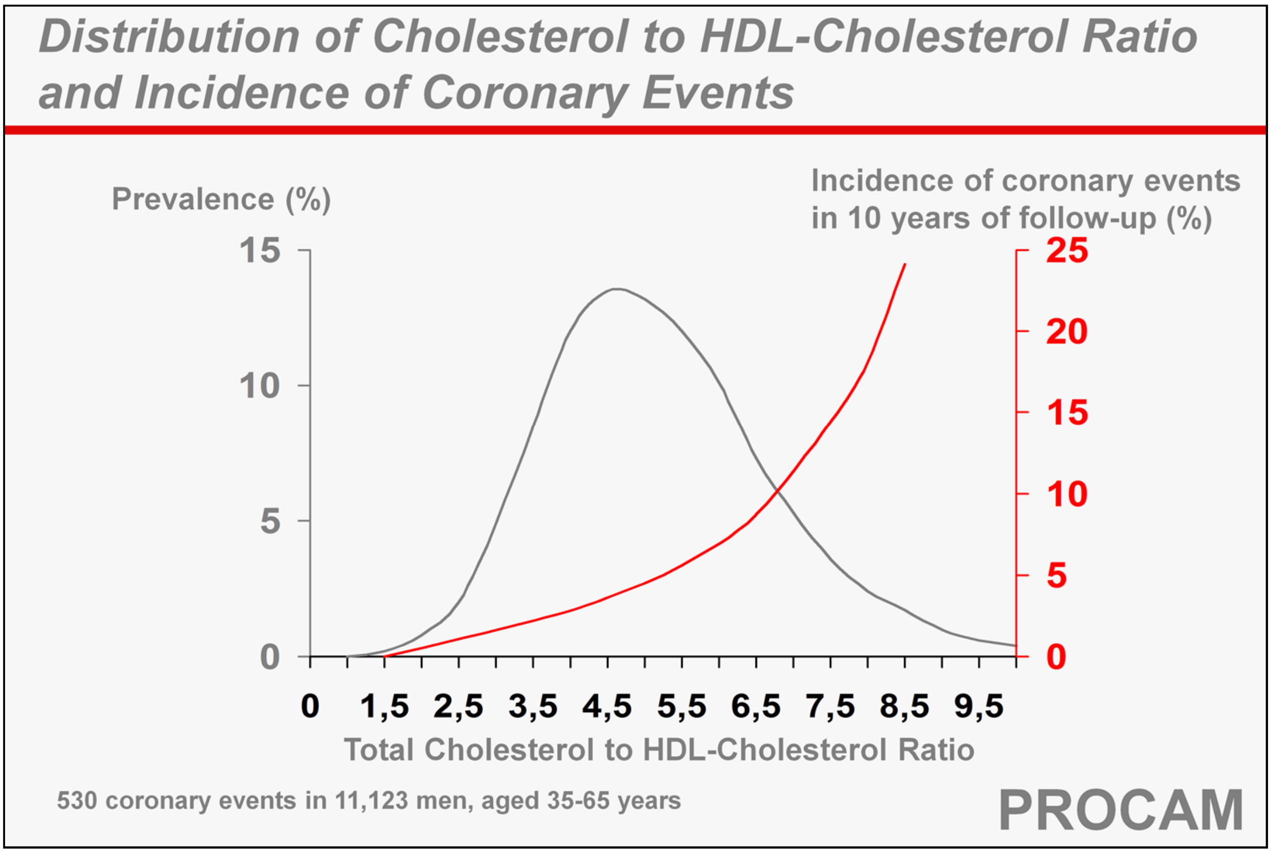
In the PROCAM Study the cohort of 11,675 men aged 35-65 years included a sufficient number of coronary events for valid statistical analysis on 10-year follow-up. The outcome characteristics of this cohort are shown on this slide. 10,593 men survived 10 years without definite nonfatal MI or stroke, 530 definite coronary events occurred. Thus, the total size of this cohort is 11,123 (530 plus 10,593) men. LDL-cholesterol was not determined in 333 men with triglyceride levels above 400 mg/dL, 32 of whom had coronary events. Thus for figures including data on LDL-cholesterol, the total size of the cohort was 10,790 and the number of coronary events was 498.



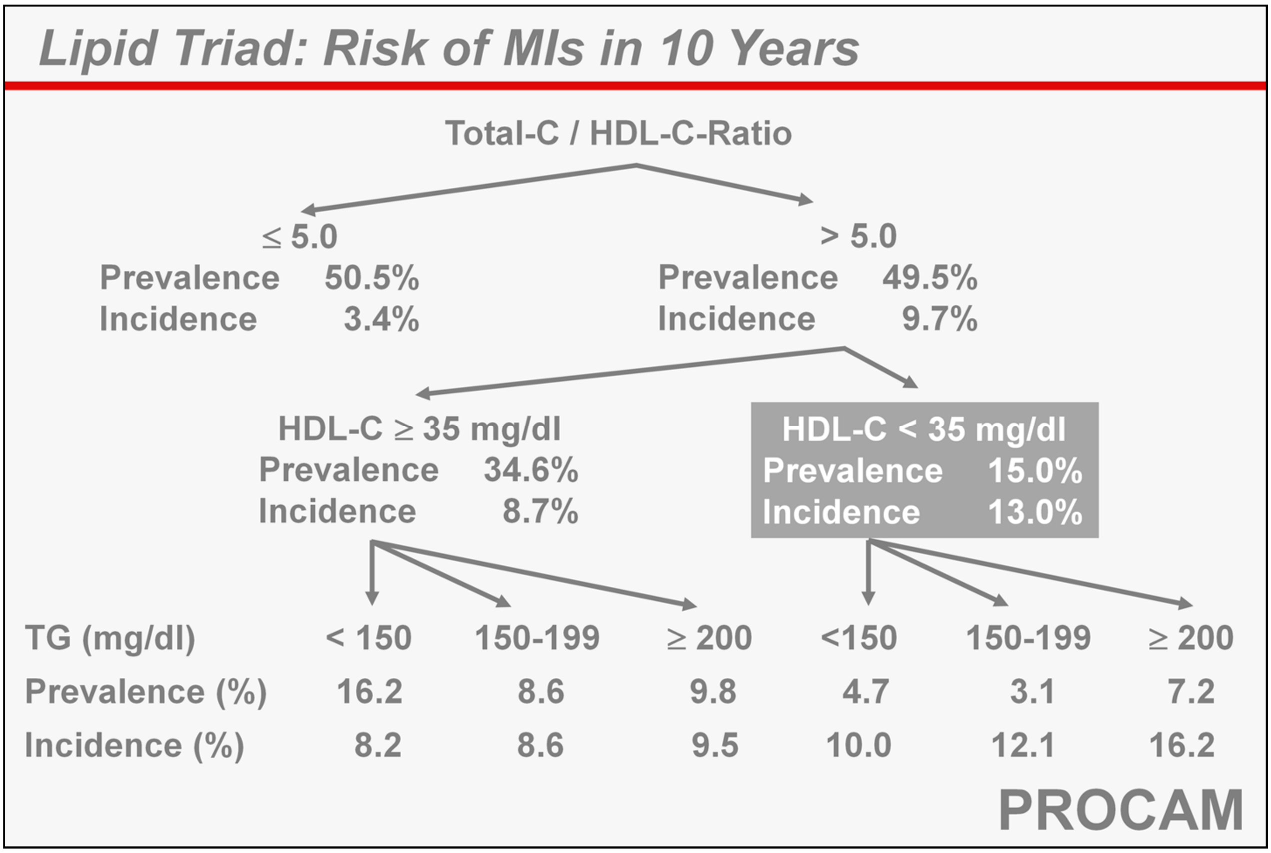
In the cohort of 11,123 men aged 35 to 65 years in PROCAM, 530 developed a coronary event (fatal or nonfatal myocardial infarction, sudden cardiac death) within 10 years of follow-up. As shown on this slide, each of the classic risk factors was between 50% and three times more common in men with a coronary event than in those without such an event.



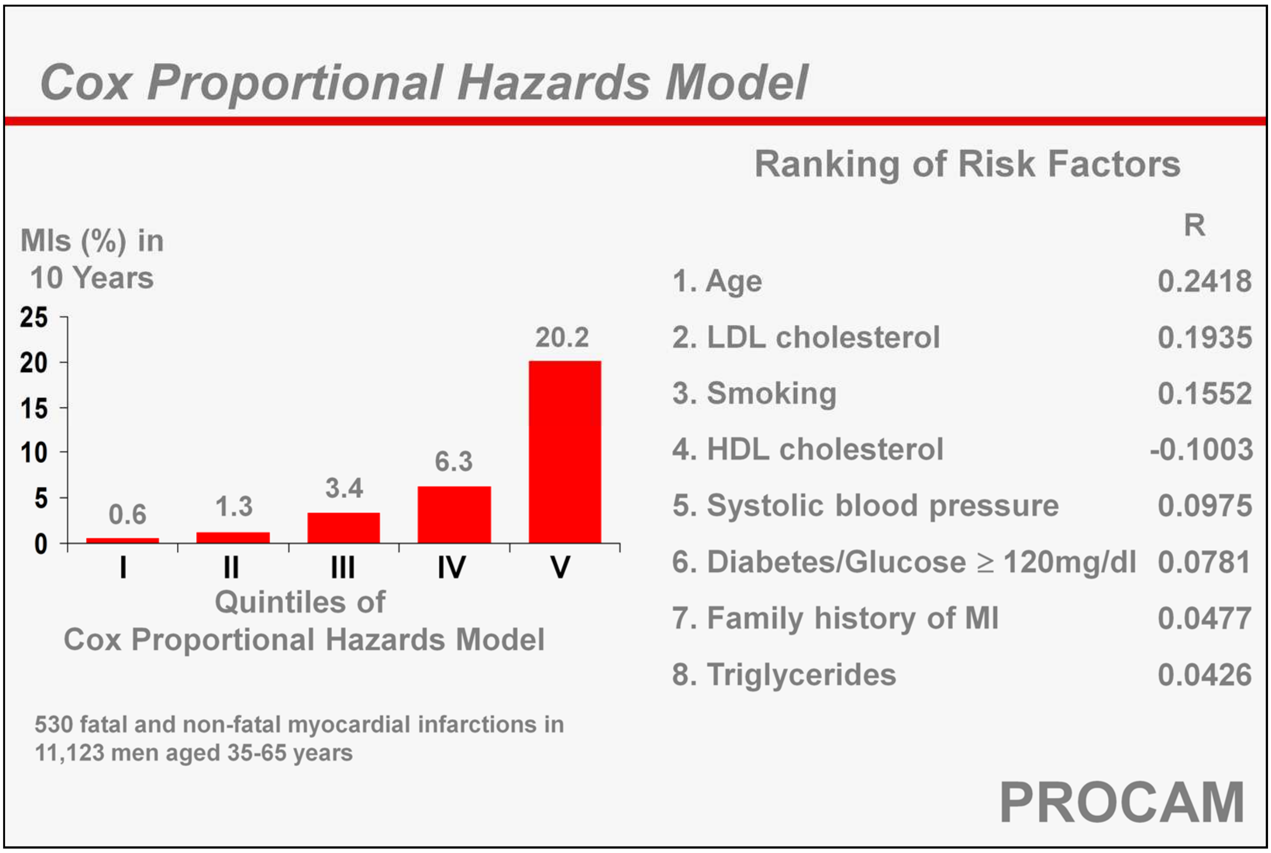
Perhaps the most important result to emerge from PROCAM and other prospective epidemiological studies of coronary heart disease risk factors is the realization that risk factors do not act in isolation, but in synergistic interaction with other risk factors. That is to say, individual risk factors interact in a multiplicative rather than an additive fashion. This is illustrated in this slide which shows the interaction between total cholesterol and HDL-cholesterol. Risk increases dramatically, from only 22 per 1000 in 10 years among men with a total cholesterol below 200 mg/dL and an HDL-cholesterol above 55 mg/dL at entry into the PROCAM Study to a striking 339 per 1000 among men with a cholesterol above 300 mg/dL and an HDL-cholesterol below 35 mg/dL. This represents a more than 15-fold differential in risk.



One of the most powerful predictors of a coronary event in PROCAM was the ratio of total to high density lipoprotein (HDL) cholesterol. This slide shows the prevalence of total / HDL-cholesterol ratios among the cohort of 10,790 men aged 35 to 65 years. The distribution of this parameter was slightly skewed to the left, with a median at 5.0. The incidence of coronary events rises steeply with an increasing ratio of total to HDL-cholesterol. At the 90. percentile of the distribution of the cholesterol to HDL-cholesterol ratio (7.33), the incidence of coronary events was 21.3 % in 10 years of follow-up. This translates to an annual incidence of 2.6 %. At the 95. percentile (8.21), the annual incidence was 3.4 %.



In recent years, much attention has been devoted to the so-called metabolic syndrome, a complex comprising insulin resistance, obesity, hypertension, and dyslipidemia. 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, see slide 5), and then further segregated according to the HDL-cholesterol and triglyceride levels, a striking gradient of risk was observed, ranging from 8.2% among men with an HDL-cholesterol above 35 mg/dL (0.9 mmol/L) and a triglyceride level of below 150 mg/dL (1.7 mmol/L) to 16.2% 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).

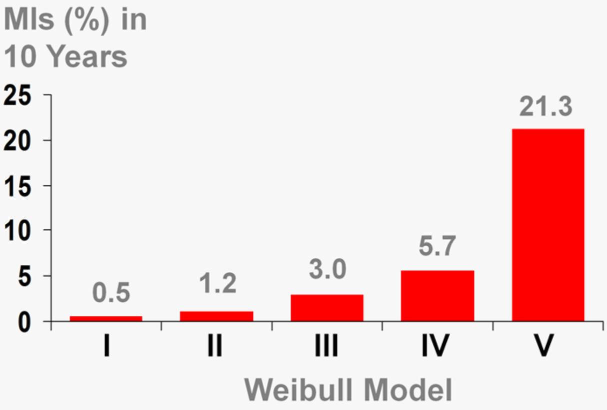


If the results of the PROCAM Study had to be summed up in one slide, this would be it. What this slide shows is the incidence of coronary events occurring within 10 years of follow-up in men aged 35 to 65 in PROCAM, divided into fifths (quintiles) using a Cox Proportional Hazards model derived from more than 50 variables measured in each man. The 8 variables listed here each make an independent contribution to risk. Taken together, they allow a more than 33-fold stratification of risk between the lowest and the highest quintile. The mean annual risk in each quintile is as follows:

- quintile 1: 0.06 %
- quintile 2: 0.13 %
- quintile 3: 0.35 %
- quintile 4: 0.65 %
- quintile 5: 2.23 %

Allocation of your patients to these quintiles can be performed using the interactive program on this Website using this link (http://www.chd-taskforce.com/calculator/calculator.htm).

Weibull Model

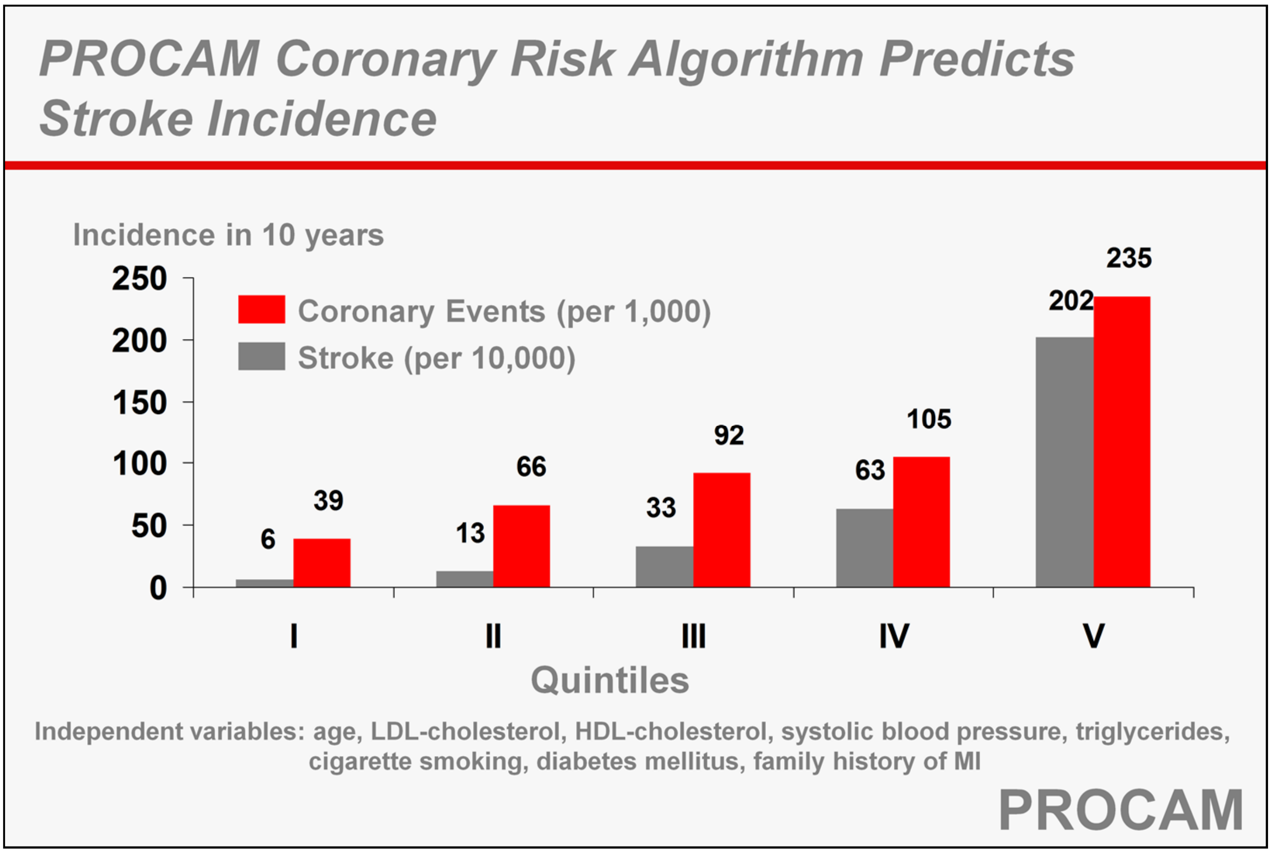


627 coronary events among
22,798 men (age 16-65 years at entry)

Ranking of Risk Factors

	R
1. Smoking	0.2097
2. LDL cholesterol	0.2009
3. Diabetes/Glucose ≥ 120mg/dl	0.1313
4. HDL cholesterol	-0.1163
5. Systolic blood pressure	0.0848
6. Family history of MI	0.0420
7. Triglycerides	0.0380

PROCAM



An important result of the PROCAM Study was the finding that the risk algorithm for coronary events also identified those men at high risk for stroke. As shown on this slide, the rate of increase in risk across the quintiles of the PROCAM algorithm was similar for coronary and cerebrovascular disease.

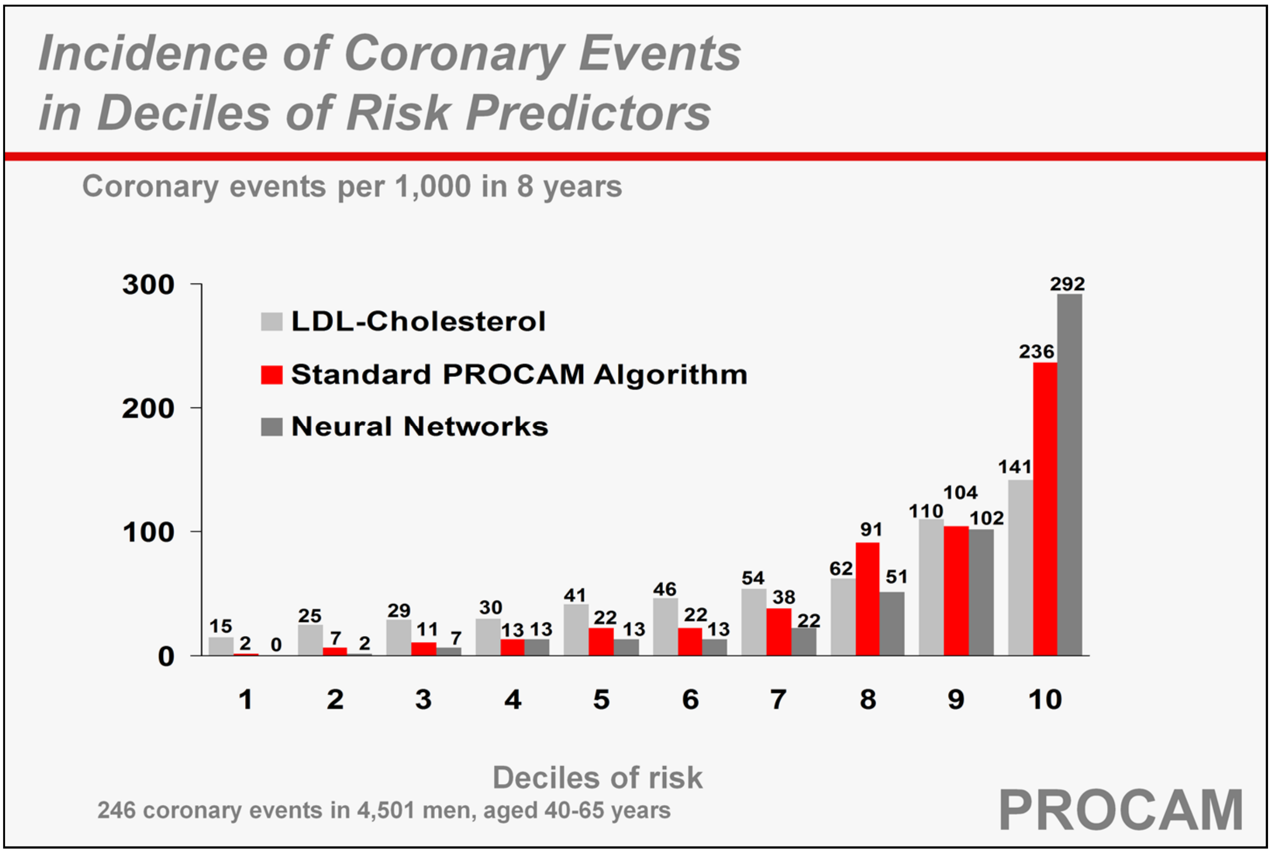
Risk Factors Included in Standard PROCAM Algorithm and Neural Network Analysis

Neural Networks	Standard PROCAM Algorithm
Age	Age
Systolic and Diastolic Blood Pressure	Systolic Blood Pressure
Antihypertensive Treatment	
HDL-C and LDL-C	HDL-C and LDL-C
Triglycerides	Triglycerides
No. of cigarettes/day	Cigarette Smoking (yes/no)
Diabetes, Fasting Blood Glucose	Diabetes (yes/no)
Body Mass Index	
Family History of MI	Family History of MI

PROCAM

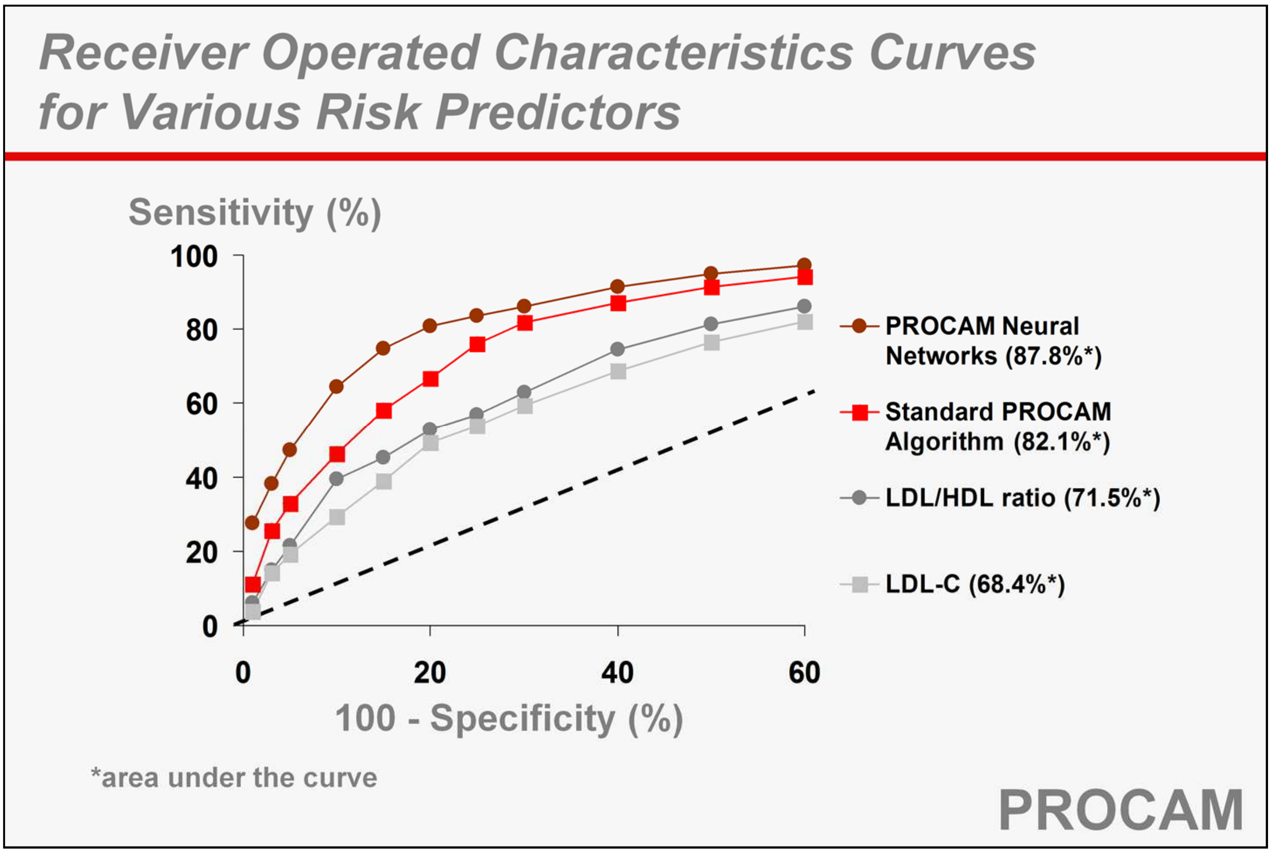
The Future of Risk Analysis:

A most promising approach to risk prediction is the use of neural networks to detect and exploit complex, non-linear interactions between risk variables. In the PROCAM Study, such neural network analysis allowed utilization of several variables which are shown on this slide.



Improvement of Risk Prediction using Neural Networks:

As shown by the PROCAM Study, a logistic regression model (standard PROCAM algorithm) using 8 variables significantly improves risk prediction compared to a single risk factor such as LDL-cholesterol. Neural network improves the ability to predict risk even further. As shown in this slide, neural network analysis allocates a greater proportion of coronary events to the highest decile of risk.



Perhaps the best measure of the performance of a predictive function is the area under receiver operated characteristics (ROC)-curves. A test which perfectly discriminates between affected and non-affected individuals passes through the top left hand corner of the graph (area under curve 100%). A test with no discriminatory power follows the dashed line shown on this slide (area under curve 50%) The better a test, the more the ROC-curve deviates from this line. As can be seen on this slide the area under the ROC-curve is significantly greater with neural network analysis compared to the standard PROCAM algorithm or single risk factors.